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**Review Article**

# A Review: Oral Antidiabetic Drugs

**Govind Kushwaha*, Priya Patel, Shahbaz Ahmad, Ankur Sharma**

**Department of Pharmaceutics, Shrinathji Institute of Pharmacy, Nathdwara**

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**Corresponding author: Govind Kushwaha**

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**Abstract:**

Diabetes mellitus is a metabolic disorder caused due to insufficiency of insulin; type 2 (T2DM) is the most prevalent form of diabetes. The prevalence of diabetes is growing rapidly worldwide; India has the second highest number of people with diabetes in the world. The main goal in diabetes management is to improve patient's quality of life, this can be achieved with better glycemic management and minimizing complications caused by hyperglycemia.

Metformin drug has been shown to prevent diabetes in people who are at high risk and decrease most of the diabetic complications. Recent report on metformin, not only indicate some implication such as renoprotective properties have been suggested for metformin, but some reports indicate its adverse effects as well that are negligible when its benefits are brought into account. The present review summarizes the various antidiabetic drugs for the treatment of diabetes mellitus.

**Keywords:** Diabetes mellitus, Antidiabetic drugs, Metformin, Blood glucose

## INTRODUCTION

Diabetes mellitus (DM) is a complex chronic illness associated with a state of high blood glucose level, or hyperglycemia, occurring from deficiencies in insulin secretion, action, or both. If high-quality care is not provided, the chronic metabolic imbalance associated with this disease puts patients at risk for long-term macro-and microvascular problems, which can increase the risk for cardiovascular disease (CVDs) frequent hospitalization, and other consequences. The four-plasma glucose (PG) criteria- (i) fasting plasma glucose (FPG) (<126mg/dL), (ii) 2-hour PG during a 75-g oral glucose tolerance test (OGTT) (<200 mg/dL), (iii) random PG (<200 mg/dL) with classic hyperglycemia signs and symptoms, or (iv) haemoglobin A1C level >6.5%- are required for the clinical diagnosis of diabetes. The American Diabetes Association (ADA) recently recommended against favouring one test over another for diagnosis. Regardless of body weight, it is advised to test all people starting at age 45. Asymptomatic adults who are overweight or obese, appear with a diagnostic symptom, and have at least one additional risk factor for developing diabetes should also be tested. Type 2 diabetes mellitus (T2DM) can co-occur with other illness including pancreatic disease linked to cystic fibrosis or gestational diabetes that

manifests during the second or third trimester of pregnancy. T2DM can also be brought on by iatrogenic factors, such as the inpatient use of glucocorticoids or the use of highly potent antiretroviral medications like protease inhibitors and nucleoside reverse transcription inhibitors in HIV- positive people. Thiazide diuretics, atypical antipsychotic medications, and statins can all lead to the development of chemical diabetes or impaired glucose tolerance (IGT).

Since type 2 diabetes mellitus is a frequent and spreading condition, it is a significant global public health issue. According to the International Diabetes federation, 387 million individuals worldwide have been diagnosed with diabetes. Diabetes was diagnosed in 29.1 million adults in the US in 2012, or 9.3% of the population, according to the Centres for Disease Control and prevention. 86 million people had prediabetes in the same year, and 15-30% of them went on to develop full-blown diabetes. Generally speaking, 1.4 million newly diagnosed cases are recorded in the US each year. Diabetes patients are more likely to experience significant health such myocardial infarction, stroke, renal failure, eyesight loss, and early death. If decisive action is not taken, the World Health Organisation predicts that the number of deaths attributable to diabetes would treble by 2030.

Both type of diabetes affects people of all ages, therefore the traditional presentations that type 2 diabetes (T2DM) exclusively affects adults and type 1 diabetes (T1DM) only affects children are not totally accurate. Patients with T2DM can experience the severe consequence known as diabetic ketoacidosis (DKA). The most common symptoms of T1DM in children are polyuria and polydipsia, and about one-third of them also have DKA, which may be the initial presenting symptom. The heterogeneity of the presentations should be kept in mind while caring for the patient with T2DM.

**Clinical Diagnosis of Type 2 Diabetes**

Diabetes can be detected in low-risk people who test their blood sugar on their own during routine primary care, in people who are assessed for their risk of developing the disease, and in patients who are simply symptomatic. Blood tests that assess PG levels can be used to diagnose T2DM early. The most popular test for identifying diabetes is the FPG; a reading of 126 mg/dL or 7.0 mmol/L verified by repeating the test a different clinic visit reliably identifies the condition. Fasting for at least eight hours is necessary for this test, and morning blood draws result in higher reliability. Another need is patient's 2 h PG of less than 200mg/dL (11.1 mmol/L) when they exhibit classic polyuria, polydipsia and /or unexplained weight loss. After a glucose load of 75g of glucose solution in water, a positive 2-h OGTT will display a PG level of 200 mg/dL or 11.1 mmol/L. Even though the two-hour PG OGTT is or more sensitive than the FPG test, it is less convenient for patients and more expensive, hence it is not frequency utilised in clinics. Additionally, this test is less important during routing follow-ups after a diabetes diagnosis has been confirmed.

The glycated haemoglobin (HbA1C) test has a good predictive value for diabetic complications and was previously used primarily to monitor the effectiveness of glycemic control. The patient's blood glucose level over a period of 3-4 months, which corresponds with the RBCs life span, is reflected by the chronic hyperglycemia marker HbA1C. However, the International Expert Committee advised using it to diagnose T2DM but not T1DM or gestational diabetes in 2009 once it had achieved standardization. A normal HbA1C

level is less than 5.7% when it is expressed as a percentage. The biggest convenience that the HbA1C test gives patients over blood glucose tests is that is doesn't call for fasting and may be completed at any time of the day. However, the cost of this test is higher, and it might not be widely accessible everywhere, which might limit its applicability. In cases of anaemia, hemolysis, other hemoglobinopathies including sickle cell disease, and haemoglobin (Hb) variations like HbC, HbE, and HbD, as well as increased foetal haemoglobin, the HbA1C test may not be accurate. Thus, consideration of these factors is warranted when doing a HbA1C test on individual of South Asian, Mediterranean, or African heritage. Only blood glucose measurement should be used to diagnose diabetes under circumstances when RBC breakdown is enhanced, including advanced pregnancy trimesters, recent bleeding, intravascular hemolysis, transfusion, and erythropoient medication. There is not much evidence to back up the diagnosis of T2DM in kids and teenagers using the A1C. The ADA recommends HbA1C for the diagnosis of T2DM in children and adolescents, even if A1C is not recommended for the diagnosis of diabetes in children with cystic fibrosis or symptoms that presage the development of acute onset of T1DM.

**Clinical Management of Type 2 Diabetes**

An early assessment of the patient's risk factors, the existence or absence of diabetes complications, and an initial review of prior treatments are necessary for comprehensive care for a patient with diabetes. This will make it possible for a patient with diabetes. This will make it possible for medical professionals to manage individuals with diabetes or prediabetes in the best possible way. The fundamentals of diabetes managements include pharmacological medication, frequent blood glucose testing, and lifestyle intervention.

**Lifestyle measures**

Based on clinical inquiries, choosing a healthier lifestyle can delay or prevent the onset of diabetes and cut risk by 58% over three years. The ADA strongly advises that individuals with IGT, IFG, or HbA1C levels of 5.7-6.4% receive counselling on making dietary and activity adjustments as well as other lifestyle improvements. However, it is advised that individuals who have already been diagnosed with diabetes seek certified dietitian nutrition counselling. A nutrient-rich balanced diet that total calories and free carbohydrates may assist people reduce weight. However, diabetes who follow a low-carbohydrates diet should be aware of potential side effects that include hypoglycemia, headache, and constipation. Other studies suggested whole grains and complex fiber in diets to enhance glycemic control. Studies show that exercise may improve patient's overall health and glycemic management, whether or not there is a corresponding reduction in body weight. It is seen as being essential for controlling and avoiding both diabetes and prediabetes. The U.S. Department of Health and Human Services advises adults over the age of 18 to engage in at least 150 minutes per week of moderate intensity exercise or 75 minutes per week of vigorous physical activity spread over at least three days per week, with no more than two days without exercise. Moderate alcohol consumption and sodium intake reduction should be taken into account in the treatment plan for diabetes patients, especially in those who have comorbid conditions like hypertension, habitual tobacco, and immunisation deficiencies (for influenza, diphtheria, pertussis, tetanus, pneumococcal, and hepatitis B). Alcohol consumption, especially while a fast, can lead to life-

threatening hypoglycemia and coma, hence patients should have specifically advised against it during. In addition, it's crucial to provide patients with counselling, psychosocial support, and education in order to successfully combat diabetes' adverse effects.

**Pharmacological Management**

**Indications**

For diabetes mellitus to be maintained most effectively, a multidisciplinary strategy is required that includes pharmaceutical therapy when necessary to achieve specific glycemic objectives in addition to dietary and activity adjustments. For the best glycemic control, doctors must advice patients to use modification to their lifestyle together with oral medications, especially as type 2 diabetes mellitus worsens with ongoing loss of pancreatic beta-cell activity and insulin production.

**Oral Hypoglycemic Medication**

- Sulfonylureas (glipizide, glyburide, gliclazide, glimepiride)
- Meglitinides (repaglinide and nateglinide)
- Biguanides (metformin)
- α-Glucosidase inhibitors (acarbose, miglitol, voglibose)
- DPP-4 Inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin)
- Thiazolidinediones (rosiglitazone, pioglitazone)
- Cycloset (bromocriptine)

Type 2 diabetes mellitus is the main condition for which oral hypoglycemic medications have FDA-approved indication for usage.

Treatment of gestational diabetes mellitus, prevention of ovarian hyperstimulation syndrome in PCOS patients undergoing intracytoplasmic sperm injection (ICSI) or in vitro fertilisation (IVF), treatment of polycystic ovary syndrome (PCOS) with menstrual irregularities, and management of antipsychotic-induced weight gain are all non-FDA approved uses for oral hypoglycemic medications like metformin.

**Mechanism of Action**

**The sulfonylureas** lower the blood glucose through an increase in secretion of insulin from the pancreatic beta cells. They may also have other extra-pancreatic hypoglycemic actions that are important prolonged therapy.

In the beta cells of the pancreas, sulfonylureas bind to adenosine triphosphate-sensitive potassium channels (K-ATP channels). This causes the channels to be inhibited and changes the resting membrane potential of the cell, which results in an influx of calcium and stimulates insulin secretion.

**Meglitinides** function similarly to sulfonylureas by controlling adenosine triphosphate-sensitive potassium channels in pancreatic beta cell, increasing insulin secretion. They do this via acting on various pancreatic beta-cell receptors.

**Metformin**: Adenosine monophosphate-activated protein kinase activity in the liver is increases by metformin, which decreases gluconeogenesis and lipogenesis in the liver and enhance insulin-mediated glucose absorption in muscles.

**Thiazolidinediones** increases the level of adiponectin, a cytokine secreted by fat tissues, which increases not only the number of insulin-sensitive adipocytes but also stimulates fatty acid oxidation. PPAR-is a nuclear receptor that is activated by thiazolidinediones. It increases peripheral glucose uptake and insulin sensitivity.

**Alpha-glucosidase inhibitors:** The intestinal brush border cells that digest

dietary starch contain alpha-glucosidase inhibitors. This prevents polysaccharides reabsorption and the conversion of sucrose to glucose and fructose.

**DPP-4inhibitors** prevent the activity of the DPP-4 enzyme. These inhibit several hormones, including glucagon-like peptide 1 (GLP-1), the glucose dependent insulinotropic polypeptide (GIP), and others. As a result, these have many effects that affect glucose management, including reduced glucagon release, increased glucose-dependent insulin release, reduced stomach emptying, and increased satiety.

**Cycloset:** The hypothalamic circadian rhythm is reset by cyclist, a sympatholytic dopamine D2 receptor agonist, which may have been affected by obesity. Through this action, insulin resistance is reversed, and the synthesis of glucose is reduced.

**Administration**

**Glipizide**: take a 2.5 mg o 10 mg pill of glipizide, either all at once or in two doses, 30 minutes prior to breakfast. Glimepiride comes in pills of 1,2, or 4 mg which should be taken once or twice with meals. The starting dose may be as low as 0.5 mg per day for people who are more susceptible to hypoglycemia, such as older patients or those with chronic kidney disease.

**Repaglinide** comes in pills of 0.5 mg, 1 mg, or 2mg, and is administration orally twice to three times day in divided dosages.

**Metformin** The first medication of choice for those with type 2 diabetes is metformin. Twice daily, 500-1000 mg pills containing it are administered orally.

**Alpha-glucosidase inhibitors**: Tablets containing 25,50, or 100 mg of alpha-glucosidase inhibitors can be taken three times per day, right before meals.

Linagliptin, a DPP-4 inhibitors comes in a 5 mg dosage. Sitagliptin is used as 25 mg, 50 mg, or 100 mg once daily; Vildagliptin is administered as 50 mg once or twice weekly; and saxagliptin is administered as 2.5 mg or 5 mg once daily after an initial dose of 0.8 mg once daily.

**Adverse Effects**

The following are adverse effects of various hypoglycemic drugs:

**Sulfonylureas:** Syncope (less than 3%), dizziness (2%-7%), nervousness, anxiety (4%), depression (<3%), insomnia (<3%), pain (<3%), paresthesia (less than 3% ), drowsiness(2%), headache , diaphoresis, hypoglycemia, pruritus, increased lactate dehydrogenase, diarrhoea, flatulence, dyspepsia, and vomiting.

**Repaglinide:** Weight gain, headache, upper respiratory tract infection, hypoglycemia, and cardiovascular ischemia.

**Metformin:** Diarrhoea (12-53%), nausea and vomiting ( 7-26% ), flatulence, chest discomfort, flushing, palpitations, headache, chills, dizziness, taste disorder, diaphoresis, nail disease, skin rash, and vitamin B 12 deficiency are only a few examples of gastrointestinal distress. Additionally, it includes lactic acidosis in less than 1 % of patients, which can be fatal and is triggered by factors that increase the risk of hypoperfusion and hypoxemia, like severe renal failure.

**Thiazolidinediones:** Edoema (less than or equal to 27%), hypoglycemia (less than or equal to 27%), cardiac failure (less than or equal to 8%), headache, bone fracture ( less than or equal to 5% ), myalgia ( less than or equal to 5% ).

**Alpha-glucosidase inhibitors:** The most common negative effects include elevated serum transaminases (less than or equal to 4%), diarrhoea (33%), gastrointestinal pain (19%), and flatulence (74%), which tends to get better over time.

**DPP-4 inhibitors:** Hypoglycemia (1%), nasopharyngitis (5%), elevated serum creatinine, severe pancreatitis, and acute renal failure are side effects of sitagliptin.

**Saxagliptin:** Acute pancreatitis (7%), lymphocytopenia (2%), hypoglycemia (6%), headache (7%), and peripheral oedema (4%).

**Linagliptin:** Acute pancreatitis (7%), nasopharyngitis (7%), elevated serum lipase ( 8%; more than three times upper limit of normal ), and hypoglycemia.

**SGLT-2 inhibitors:** Insomnia, fungal vaginosis, urinary tract infection, increased urine output, dysuria, influenza, bone fracture, and renal impairment, dyslipidemia, hyperphosphatemia, hypovolemia, and nausea are other conditions that might causes these symptoms.

**Cycloset:** weakness, headache, nausea, rhinitis, constipation, and dizziness**.**

**Monitoring**

- Patients with good blood sugar control have their fasting, pre-meal and haemoglobin A1C levels examined twice a year, whereas those who did not accomplish their treatment goals or underwent a chance in medication have their levels checked every three months.
- Haemoglobin, RBC indices, and renal function tests should be checked before treatment beings and at least once a year in individuals on metformin. If the glomerular filtration rate is between 45 and less than 60 mL/min/1.73 m2, the doctor should repeat these tests every to six months, and every three months if it is between 30 and less than 45 mL/min/1.73 m2. If the patient is on metformin for a prolonged period of time serum vitamin B12 and folate levels should be checked to rule out megaloblastic anaemia.
- Aspartate transaminase, alanine transaminase, alkaline phosphatase, and total bilirubin are tested in patients on pioglitazone both before and after treatment begins. Monitoring in patients is necessary for signs and symptoms of heart failure, weight increase, characteristics indicative of bladder cancer (hematuria, dysuria, and urine urgency), and routine ophthalmologic exams.
- Note any signs and symptoms of hypoglycemia abnormal liver function, and weigh fluctuations (due to the potential to cause weight gain) in patients taking sulfonylureas.
- Every three months throughout the first year of treatment and on occasion after that, the level of serum creatinine and serum transaminase in acarbose-taking patients should be checkout.
- For patients using SGLT2 inhibitors, monitoring of renal function and LDL is necessary.

## CONCLUSION

Metformin is an anti-diabetic drug in the biguanide class for the treatment of type 2 diabetes mellitus, in particular in overweight and obese people and those with normal kidney function.

Metformin has several benefits in patients with type 2 diabetes mellitus, including decreased hyperinsulinemia, weight reduction, augmented fibrinolysis, improved lipid profile and enhanced endothelial function.

Although the use of Metformin in diabetes has its safety concerns, its benefits and the recent results indicate that the nephroprotective activity against nephrotoxic agents on metformin and its recent good safety records have led researchers to consider the use of this drug more and more in insulin resistance states

even before the development of hyperglycemia.

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