RESEARCH PORTAL CENTRAL

Journal of Medical Research and Clinical Case Reports

OPEN ACCESS

Review Article

Antidiabetic Drugs: Classification, Mechanism of Action, Therapeutic Application, and Recent Advance in Diabetes Management

Vivek Dinanath Parab[1]*, Dattaram Ashok Parab[1], Jatin Suhas Surve[1], Pratham Dnyanesh Vetkar[1], Milind Dadasaheb Chormule[1], Sahil Suhas Harne[1], Utkarsh Dashrath More[1]

1. Vijayrao Naik college of pharmacy, shirval, Kankavli – 416602, Maharashtra, India.

How to cite this article: Vivek D. Parab, Dattaram A. Parab, Jatin S. Surve, Pratham D. Vetkar, Milind D. Chormule, et al. (2026). Antidiabetic Drugs: Classification, Mechanism of Action, Therapeutic Application, and Recent Advance in Diabetes Management. Journal of Medical Research and Clinical Case Reports, RPC Publishers. 3(1),1-15.

***Address for correspondence:** Vivek Dinanath Parab, Vijayrao Naik college of pharmacy, shirval, Kankavli – 416602, Maharashtra, India.

Email: vivek8523parab@gmail.com

Submitted: April 11, 2026
Approved: May 14, 2026
Published: May 25, 2026

Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both. It has emerged as one of the most serious global health challenges, with a rapidly increasing prevalence due to urbanization, sedentary lifestyles, dietary changes, obesity, and aging populations. According to the International Diabetes Federation, hundreds of millions of individuals worldwide are currently affected by diabetes, with Type 2 diabetes mellitus accounting for the majority of cases. Persistent hyperglycemia is associated with severe long-term complications including cardiovascular disease, nephropathy, neuropathy, retinopathy, and increased mortality. The management of diabetes requires a comprehensive approach involving lifestyle modification, dietary regulation, physical activity, and pharmacological therapy. Antidiabetic drugs play a crucial role in maintaining glycemic control and preventing disease progression and complications. Over the past few decades, significant advancements have been made in the development of antidiabetic agents targeting different pathophysiological mechanisms of diabetes. These include insulin preparations, insulin secretagogues, insulin sensitizers, incretin-based therapies, inhibitors of intestinal carbohydrate digestion, and agents that promote renal glucose excretion. Currently available antidiabetic drugs act through multiple mechanisms such as stimulation of pancreatic insulin secretion, enhancement of insulin sensitivity in peripheral tissues, inhibition of hepatic glucose production, delay of intestinal glucose absorption, and modulation of incretin hormones. Modern pharmacotherapy has also expanded to include novel drug classes such as sodium–glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, which not only improve glycemic control but also provide additional benefits including weight reduction and cardiovascular protection. This review provides a comprehensive overview of antidiabetic drugs including their classification, mechanisms of action, pharmacological properties, therapeutic applications, adverse effects, and recent advancements in diabetes management. Furthermore, emerging therapeutic approaches such as combination therapy, novel drug delivery systems, and innovative pharmacological targets are discussed. A better understanding of these therapeutic strategies may contribute to improved clinical outcomes and more effective management of diabetes mellitus.

Keywords: diabetes mellitus; insulin therapy; insulin resistance; β-cell dysfunction; incretin-based therapy; SGLT-2 inhibitors; GLP-1 receptor agonists

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The disease is associated with disturbances in carbohydrate, lipid, and protein metabolism and leads to progressive damage of various organs, particularly the eyes, kidneys, nerves, heart, and blood vessels. Due to its increasing prevalence and associated complications, diabetes mellitus has become a major global public health concern. Globally, the prevalence of diabetes has increased dramatically during the past few decades. According to international health estimates, hundreds of millions of individuals worldwide are currently living with diabetes, and this number is expected to increase significantly in the coming years due to factors such as urbanization, aging populations, sedentary lifestyles, unhealthy dietary habits, and rising obesity rates. Type 2 diabetes mellitus (T2DM) accounts for approximately 90-95% of all diabetes cases and is primarily associated with insulin resistance combined with progressive pancreatic β-cell dysfunction. Diabetes mellitus can be broadly classified into several categories including Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and other specific types of diabetes caused by genetic defects, pancreatic diseases, endocrine disorders, or drug-induced conditions. Type 1 diabetes is an autoimmune disorder characterized by destruction of pancreatic β-cells leading to absolute insulin deficiency. In contrast, Type 2 diabetes results from a combination of insulin resistance in peripheral tissues and inadequate insulin secretion by pancreatic β-cells [1,2].

Chronic hyperglycemia associated with diabetes contributes to the development of both microvascular and macrovascular complications. Microvascular complications include diabetic retinopathy, nephropathy, and neuropathy, whereas macrovascular complications include cardiovascular diseases such as coronary artery disease, stroke, and peripheral vascular disease. These complications significantly increase morbidity and mortality among diabetic patients and impose a substantial economic burden on healthcare systems worldwide. Effective management of diabetes focuses on maintaining optimal glycemic control and preventing long-term complications. Current treatment strategies involve a combination of lifestyle modification, dietary management, regular physical activity, and pharmacological therapy. Antidiabetic drugs are essential components of diabetes management and act through various mechanisms including stimulation of insulin secretion, improvement of insulin sensitivity, inhibition of glucose absorption from the intestine, and increased excretion of glucose through the kidneys. Over the past few decades, remarkable progress has been made in the development of novel antidiabetic agents targeting different metabolic pathways involved in glucose homeostasis. In addition to traditional therapies such as insulin, sulfonylureas, and biguanides, newer drug classes including incretin-based therapies, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and other emerging agents have significantly expanded the therapeutic options available for diabetes management. These modern drugs not only improve glycemic control but also provide additional benefits such as weight reduction, cardiovascular protection, and improved patient adherence. Therefore, a comprehensive understanding of the classification, mechanisms of action, pharmacological properties, and clinical applications of antidiabetic drugs is essential for effective diabetes management. This review aims to provide an in-depth overview of currently available antidiabetic drugs, their mechanisms of action, therapeutic benefits, adverse effects, and recent advances in diabetes pharmacotherapy [3,4].

Pathophysiology Of Diabetes Mellitus

Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia resulting from abnormalities in insulin secretion, insulin action, or both. The pathophysiology of diabetes involves multiple metabolic and hormonal disturbances affecting glucose homeostasis. In Type 2 diabetes mellitus (T2DM), the disease develops progressively due to a combination of insulin resistance in peripheral tissues and impaired pancreatic β-cell function, leading to inadequate insulin production relative to metabolic demands. These metabolic abnormalities disrupt normal glucose metabolism and result in persistent elevation of blood glucose levels [5].

Glucose Homeostasis: Glucose homeostasis refers to the regulation of blood glucose concentration within a narrow physiological range, typically 70-110 mg/dL during fasting conditions. This balance is maintained through a complex interplay between several organs, primarily the pancreas, liver, skeletal muscles, adipose tissue, kidneys, and gastrointestinal tract, under the regulation of hormones such as insulin and glucagon. Insulin, a peptide hormone secreted by the pancreatic β-cells of the islets of Langerhans, plays a central role in lowering blood glucose levels. It facilitates the uptake of glucose by insulin-sensitive tissues such as skeletal muscles and adipose tissue through activation of glucose transporter proteins (GLUT-4). Insulin also suppresses hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis in the liver. In contrast, glucagon, secreted by pancreatic α-cells, acts as a counter-regulatory hormone that increases blood glucose levels. It stimulates hepatic glucose production through activation of glycogenolysis and gluconeogenesis pathways during fasting or hypoglycemic states. The balance between insulin and glucagon ensures stable glucose concentrations under both fed and fasting conditions. In individuals with diabetes, this regulatory mechanism becomes impaired. Reduced insulin secretion or decreased insulin sensitivity leads to inadequate glucose uptake by peripheral tissues and increased hepatic glucose production, resulting in chronic hyperglycemia [5,6].

Insulin Resistance

Insulin resistance is a key pathological feature of Type 2 diabetes mellitus and refers to a reduced biological response of target tissues to normal circulating levels of insulin. It primarily affects skeletal muscle, liver, and adipose tissue, which are the major sites of glucose metabolism. In skeletal muscle, insulin resistance results in impaired glucose uptake due to defects in insulin signaling pathways and reduced translocation of GLUT-4 transporters to the cell membrane. Since skeletal muscle accounts for the majority of postprandial glucose disposal, impaired glucose uptake significantly contributes to elevated blood glucose levels. In the liver, insulin resistance leads to excessive hepatic glucose production due to continued gluconeogenesis and glycogenolysis despite elevated insulin levels. Normally, insulin suppresses hepatic glucose output; however, in insulin-resistant states, this inhibitory effect is diminished, leading to increased glucose release into the bloodstream. Adipose tissue insulin resistance results in increased lipolysis and release of free fatty acids (FFAs) into circulation. Elevated FFAs further aggravate insulin resistance in liver and muscle tissues and contribute to lipid accumulation, oxidative stress, and chronic low-grade inflammation, which are important contributors to metabolic dysfunction in diabetes [7].

β-Cell Dysfunction

Pancreatic β-cell dysfunction is another critical factor in the development and progression of diabetes mellitus. In the early stages of Type 2 diabetes, pancreatic β-cells attempt to compensate for insulin resistance by increasing insulin secretion.

However, over time, this compensatory mechanism becomes inadequate due to progressive deterioration of β-cell function and mass. Several factors contribute to β-cell dysfunction, including glucotoxicity, lipotoxicity, oxidative stress, mitochondrial dysfunction, and chronic inflammation. Persistent hyperglycemia impairs insulin gene expression and insulin secretion, a phenomenon known as glucotoxicity. Similarly, elevated free fatty acids can cause lipotoxic effects that damage β-cells and reduce insulin production. In addition, prolonged metabolic stress may lead to β-cell apoptosis and decreased β-cell mass, further reducing insulin secretion capacity. As β-cell function declines, insulin production becomes insufficient to overcome insulin resistance, leading to worsening hyperglycemia and progression of diabetes [8].

The "Ominous Octet" Concept in Type 2 Diabetes

The modern understanding of Type 2 diabetes pathophysiology was significantly advanced by the concept known as the "Ominous Octet," which describes eight major pathophysiological defects responsible for hyperglycemia in T2DM. [9] Diabetes involves multiple interconnected defects, including reduced insulin secretion from pancreatic β-cells and increased glucagon release from α-cells, along with elevated hepatic glucose production. It is further characterized by impaired brain regulation of appetite, increased lipolysis in adipose tissue, enhanced renal glucose reabsorption, a diminished incretin effect, and reduced glucose uptake in skeletal muscles. These interconnected abnormalities collectively contribute to the development of persistent hyperglycemia in Type 2 diabetes mellitus and form the basis for the development of modern antidiabetic drugs that target specific metabolic pathways involved in glucose regulation.

Understanding these mechanisms is essential for developing effective pharmacological therapies aimed at correcting metabolic abnormalities and improving glycemic control in diabetic patients [5].

Classification of Antidiabetic Drugs

Antidiabetic drugs are pharmacological agents used to control hyperglycemia in patients with diabetes mellitus. These drugs act through different mechanisms targeting various metabolic pathways involved in glucose regulation, including stimulation of insulin secretion, enhancement of insulin sensitivity, inhibition of intestinal glucose absorption, modulation of incretin hormones, and promotion of renal glucose excretion. The development of multiple drug classes reflects the complex pathophysiology of diabetes and the need to target different metabolic defects involved in the disease. Antidiabetic drugs are broadly classified into insulin preparations and non-insulin antidiabetic agents, which include both oral and injectable therapies [10].

Insulin Preparations

Insulin therapy is essential in the management of Type 1 diabetes mellitus and is also widely used in advanced stages of Type 2 diabetes mellitus when endogenous insulin production becomes insufficient. Insulin is a peptide hormone produced by the pancreatic β-cells that regulates glucose metabolism by promoting glucose uptake in peripheral tissues and inhibiting hepatic glucose production [11].

Insulin preparations are classified based on their onset of action, peak activity, and duration of action, which allows clinicians to mimic physiological insulin secretion patterns.

Table 1: Types of Insulin Preparations [12-16].

Type of Insulin	Examples	Onset of Action	Peak Effect	Duration	Clinical Use
Rapid-acting	Insulin lispro, insulin aspart, insulin glulisine	10–30 minutes	1–3 hours	3–5 hours	Control of postprandial blood glucose
Short-acting	Regular insulin	30–60 minutes	2–5 hours	6–8 hours	Routine glycemic control and emergency use such as diabetic ketoacidosis
Intermediate-acting	NPH insulin	1–2 hours	4–12 hours	12–18 hours	Basal insulin coverage
Long-acting	Insulin glargine, insulin detemir	1–2 hours	Minimal peak	About 24 hours	Steady basal glucose control
Ultra long-acting	Insulin degludec	1–2 hours	Minimal peak	More than 24 hours	Prolonged basal control with reduced hypoglycemia risk

Non-Insulin Antidiabetic Drugs

Non-insulin antidiabetic drugs are primarily used in the management of Type 2 diabetes mellitus. These agents act through different mechanisms to improve glycemic control by targeting specific defects in glucose metabolism.

Insulin secretagogues

These drugs stimulate pancreatic β-cells to increase insulin secretion.

Sulfonylureas: Sulfonylureas are among the earliest oral antidiabetic agents used in clinical practice. They act by blocking ATP-sensitive potassium (KATP) channels in pancreatic β-cells, leading to membrane depolarization, calcium influx, and subsequent insulin release. Common examples include glibenclamide (glyburide), glipizide, gliclazide, and glimepiride. Although effective in reducing blood glucose levels, they are associated with adverse effects such as hypoglycemia and weight gain. Sulfonylureas effectively reduce blood glucose levels but may cause hypoglycemia and weight gain as major adverse effects [17].

Meglitinides: Meglitinides are short-acting insulin secretagogues that stimulate insulin release in a glucose-dependent manner. They primarily control postprandial hyperglycemia due to their rapid onset and short duration of action. Examples including Repaglinide, Nateglinide

These drugs are often preferred in patients with irregular meal schedules because they can be taken before meals [18].

Insulin sensitizers

Insulin sensitizers improve the responsiveness of peripheral tissues to insulin and reduce insulin resistance.

Biguanides: The most widely used biguanide is metformin, which is considered the first-line pharmacological therapy for Type 2 diabetes mellitus. Metformin reduces hepatic glucose production by inhibiting gluconeogenesis and increases peripheral glucose uptake by activating AMP-activated protein kinase (AMPK). It also improves insulin sensitivity and may promote modest weight loss [19].

Thiazolidinediones (TZDs): Thiazolidinediones act by activating peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor involved in regulation of glucose and lipid metabolism. Examples including Pioglitazone, Rosiglitazone These drugs enhance insulin sensitivity in adipose tissue, skeletal muscle, and liver, thereby improving glucose utilization. However, their use is associated with adverse effects such as fluid retention, weight gain, and increased risk of heart failure [20].

α-Glucosidase Inhibitors: α-Glucosidase inhibitors act in the gastrointestinal tract by inhibiting enzymes responsible for carbohydrate digestion. This slows the breakdown of complex carbohydrates into glucose, thereby reducing postprandial blood glucose levels.

Examples including Acarbose, Miglitol, Voglibose. Common adverse effects include gastrointestinal disturbances such as flatulence, abdominal discomfort, and diarrhea [21].

Incretin-Based Therapies

Incretin hormones play a crucial role in glucose metabolism by enhancing insulin secretion after food intake [22].

DPP-4 Inhibitors: Dipeptidyl peptidase-4 (DPP-4) inhibitors prevent degradation of incretin hormones such as GLP-1 and GIP, thereby enhancing insulin secretion and suppressing glucagon release. Examples including Sitagliptin, SaxagliptinL, Vildagliptin, Alogliptin. These drugs have a low risk of hypoglycemia and neutral effects on body weight [23].

GLP-1 Receptor Agonists: GLP-1 receptor agonists mimic the action of endogenous glucagon-like peptide-1. They stimulate insulin secretion, inhibit glucagon release, slow gastric emptying, and promote satiety. Examples including Exenatide, Liraglutide, Dulaglutide

These agents often result in significant weight loss and improved glycaemic control.[24]

Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors: SGLT-2 inhibitors are a relatively new class of antidiabetic drugs that reduce blood glucose levels by inhibiting glucose reabsorption in the proximal renal tubules, leading to increased urinary glucose excretion.

Examples including Dapagliflozin, Canagliflozin, Empagliflozin. These drugs also provide additional benefits including weight reduction, blood pressure lowering, and cardiovascular protection [25].

Miscellaneous Antidiabetic Drugs: Some drugs act through unique mechanisms and are used as adjunct therapies.

Examples including Pramlintide - amylin analog that slows gastric emptying, Bromocriptine - dopamine agonist affecting metabolic regulation, Colesevelam - bile acid sequestrant that improves glycemic control [26].

Mechanism of Action of Antidiabetic Drugs

Antidiabetic drugs exert their therapeutic effects by targeting various physiological and molecular pathways involved in glucose metabolism. Since Type 2 diabetes mellitus is characterized by multiple metabolic abnormalities including insulin resistance, impaired insulin secretion, excessive hepatic glucose production, reduced incretin activity, and increased renal glucose reabsorption modern pharmacotherapy focuses on correcting these defects through diverse mechanisms. Understanding the molecular mechanisms of antidiabetic drugs is essential for optimizing therapeutic strategies and developing novel agents that improve glycemic control while minimizing adverse effects [27].

Insulin Receptor Signaling Pathway

Insulin exerts its biological effects by binding to the insulin receptor (IR), a transmembrane receptor belonging to the tyrosine kinase receptor family. This receptor consists of two extracellular α-subunits and two transmembrane β-subunits. Upon insulin binding, the receptor undergoes autophosphorylation of tyrosine residues, which activates intracellular signaling pathways responsible for glucose uptake and metabolic regulation [28].

Two Major Signaling Pathways are Involved

PI3K-Akt Pathway: This pathway plays a crucial role in glucose metabolism. It begins with insulin binding to its receptor, which triggers receptor autophosphorylation and subsequent activation of insulin receptor substrates such as IRS-1 and IRS-2. This leads to activation of phosphatidylinositol 3-kinase, followed by stimulation of protein kinase B. As a result, GLUT-4 glucose transporters translocate to the cell membrane, facilitating increased glucose uptake in muscle and adipose tissue. Additionally, this pathway promotes glycogen synthesis and reduces hepatic glucose production [29].

MAPK Pathway: The mitogen-activated protein kinase (MAPK) pathway regulates cell growth, differentiation, and gene expression. This pathway contributes to the long-term metabolic and anabolic effects of insulin. In Type 2 diabetes, defects in insulin signaling pathways contribute to insulin resistance, which reduces glucose uptake and promotes hyperglycemia [30].

ATP-Sensitive Potassium Channel Mechanism (Sulfonylureas and Meglitinides)

Sulfonylureas and meglitinides primarily act on pancreatic β-cells by stimulating insulin secretion. Under normal physiological conditions, glucose enters β-cells through GLUT-2 transporters and is metabolized to generate ATP. The resulting increase in ATP levels leads to closure of ATP-sensitive potassium (KATP) channels, causing membrane depolarization. This depolarization opens voltage-dependent calcium channels, allowing calcium influx, which ultimately triggers the exocytosis of insulin-containing secretory granules. Sulfonylureas mimic this natural process by directly binding to the sulfonylurea receptor (SUR1) component of the KATP channel, leading to its closure, subsequent membrane depolarization, increased calcium entry, and enhanced insulin secretion. Meglitinides act through a similar mechanism but have shorter binding duration, resulting in rapid and short-acting insulin release that mainly controls postprandial hyperglycemia [32].

AMPK Activation Pathway (Metformin)

Metformin, the most widely prescribed oral antidiabetic drug, primarily acts by activating AMP-activated protein kinase (AMPK), a key cellular energy sensor that regulates metabolic pathways.[33]

AMPK activation leads to multiple metabolic effects:

In the Liver: Metformin suppresses hepatic gluconeogenesis, thereby reducing glucose production. This effect is mediated through activation of AMP-activated protein kinase, which inhibits key gluconeogenic enzymes and leads to a reduction in hepatic glucose output [34].

In Skeletal Muscle: Metformin enhances glucose uptake by increasing GLUT-4 translocation to the cell membrane.

In Adipose Tissue: Metformin improves insulin sensitivity and reduces lipogenesis, leading to several beneficial metabolic effects. These include reduced hepatic glucose production, increased peripheral glucose utilization, enhanced insulin sensitivity, and decreased intestinal glucose absorption. This multi-target mechanism explains why metformin is considered the first-line pharmacological treatment for Type 2 diabetes.

PPAR-γ Activation Mechanism (Thiazolidinediones)

Thiazolidinediones such as pioglitazone and rosiglitazone act by activating peroxisome proliferator-activated receptor gamma, a nuclear transcription factor involved in glucose and lipid metabolism. These receptors are primarily expressed in adipose tissue, skeletal muscle, and the liver. Upon activation, PPAR-γ forms a heterodimer with the retinoid X receptor and binds to specific DNA sequences called peroxisome proliferator response elements, leading to changes in gene expression related to glucose uptake, lipid metabolism, and insulin sensitivity. As a result, there is increased expression of GLUT-4 transporters, reduced circulating free fatty acids, enhanced insulin sensitivity, and decreased inflammatory cytokines. However, excessive activation of PPAR-γ may cause fluid retention, weight gain, and an increased risk of cardiovascular complications, which can limit the clinical use of these agents [22].

Incretin Hormone Mechanism

Incretin hormones are gastrointestinal peptides that enhance insulin secretion in response to nutrient intake, with the two major hormones being glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1. These hormones are released from intestinal endocrine cells after food ingestion and play an important role in glucose regulation by stimulating

glucose-dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and increasing satiety. However, their activity is short-lived because they are rapidly degraded by the enzyme dipeptidyl peptidase-4 [36].

Two drug classes target the incretin pathway

DPP-4 inhibitors: These drugs block degradation of endogenous GLP-1 and GIP, thereby prolonging incretin activity [37].
GLP-1 receptor agonists: These drugs mimic the action of natural GLP-1 and stimulate insulin secretion while suppressing glucagon release. Both classes improve glycemic control with low risk of hypoglycemia.[38]

Renal Glucose Transport Inhibition (SGLT-2 Inhibitors)

In healthy individuals, about 90 percent of filtered glucose is reabsorbed in the proximal renal tubules by the sodium-glucose cotransporter-2 protein. SGLT-2 inhibitors lower blood glucose levels by blocking this transporter, leading to reduced glucose reabsorption, increased urinary glucose excretion, and a consequent reduction in plasma glucose concentration. In addition to glycemic control, these agents promote weight loss due to caloric loss, reduce blood pressure, and provide cardiovascular and renal protective effects. Since this mechanism is independent of insulin, SGLT-2 inhibitors remain effective even in advanced stages of Type 2 diabetes mellitus [21].

Intestinal Carbohydrate Digestion Inhibition (α-Glucosidase Inhibitors)

α-Glucosidase inhibitors exert their effect in the small intestine by inhibiting enzymes responsible for the breakdown of complex carbohydrates into absorbable glucose. This results in delayed carbohydrate digestion, reduced glucose absorption, and attenuation of postprandial hyperglycemia. Common agents in this class include acarbose, miglitol, and voglibose. However, the presence of undigested carbohydrates in the intestine may lead to gastrointestinal adverse effects such as flatulence and abdominal discomfort [39].

Pharmacological Profile of Major Antidiabetic Drug Classes

Antidiabetic drugs differ significantly in their pharmacological properties, including pharmacodynamics, pharmacokinetics, therapeutic efficacy, and safety profiles. Selection of appropriate therapy depends on several factors such as the severity of hyperglycemia, presence of comorbidities, risk of hypoglycemia, body weight considerations, and patient tolerance. Understanding the pharmacological characteristics of different drug classes is essential for optimizing diabetes management [40].

Table 2. Comprehensive Pharmacological Profile of Major Antidiabetic Drug Classes [41-48].

Drug Class	Examples	Mechanism of Action	Pharmacokinetics	Therapeutic Uses	Advantages	Adverse Effects	Contraindications / Notes
Biguanides	Metformin	Reduces hepatic gluconeogenesis, enhances insulin sensitivity, increases peripheral glucose uptake, and decreases intestinal glucose absorption through activation of AMP-activated protein kinase.	Absorbed from the small intestine with a bioavailability of approximately 50–60 percent. It is widely distributed in body tissues, undergoes minimal metabolism, and is excreted unchanged by the kidneys. The half-life is 4–8 hours.	Type 2 diabetes mellitus, prediabetes, polycystic ovary syndrome, and metabolic syndrome.	Considered first-line therapy, does not cause weight gain, and improves insulin sensitivity.	Gastrointestinal disturbances including nausea, diarrhea, and abdominal discomfort. Rarely associated with lactic acidosis.	Contraindicated in severe renal impairment, hepatic disease, heart failure, and conditions associated with hypoxia.
Sulfonylureas	Tolbutamide, Chlorpropamide, Glipizide, Glibenclamide, Glimepiride, Gliclazide	Stimulate insulin secretion from pancreatic beta cells by binding to sulfonylurea receptors and closing ATP-sensitive potassium channels.	Well absorbed from the gastrointestinal tract, highly protein bound, metabolized in the liver, and excreted through urine and bile.	Type 2 diabetes mellitus in patients with functional pancreatic beta cells, often used in combination with metformin.	Effective in reducing blood glucose levels and widely used in clinical practice.	Hypoglycemia, weight gain, gastrointestinal disturbances, and skin reactions.	Increased risk of hypoglycemia in elderly patients and in those with renal impairment.
Meglitinides	Repaglinide, Nateglinide	Stimulate rapid insulin secretion by acting on ATP-sensitive potassium channels in pancreatic beta cells with a shorter duration of action.	Rapidly absorbed with onset of action within 15 to 30 minutes and short duration of approximately 3 to 4 hours. These drugs are metabolized in the liver.	Control of postprandial hyperglycemia in type 2 diabetes mellitus.	Rapid onset of action, flexible dosing schedule, and lower risk of prolonged hypoglycemia.	Mild hypoglycemia and weight gain.	Should be administered before meals due to short duration of action.
Thiazolidinediones	Pioglitazone, Rosiglitazone	Activate peroxisome proliferator-activated receptor gamma, leading to improved insulin sensitivity and regulation of glucose and lipid metabolism.	Well absorbed after oral administration, extensively metabolized in the liver, and have a half-life of approximately 16 to 24 hours.	Type 2 diabetes mellitus associated with insulin resistance.	Improve insulin sensitivity and lipid profile.	Weight gain, fluid retention, edema, and increased risk of heart failure.	Contraindicated in patients with heart failure.
Alpha-glucosidase inhibitors	Acarbose, Miglitol, Voglibose	Inhibit intestinal alpha-glucosidase enzymes, delaying the breakdown of complex carbohydrates and reducing postprandial glucose absorption.	Act locally in the gastrointestinal tract with minimal systemic absorption.	Management of postprandial hyperglycemia in type 2 diabetes mellitus.	Minimal systemic effects and useful for post-meal glucose control.	Flatulence, abdominal discomfort, and diarrhea.	Gastrointestinal intolerance is common and may limit use.
DPP-4 inhibitors	Sitagliptin, Saxagliptin, Linagliptin, Vildagliptin, Alogliptin	Inhibit the dipeptidyl peptidase-4 enzyme, thereby increasing incretin levels, enhancing insulin secretion, and reducing glucagon secretion.	Administered orally and generally well tolerated, with pharmacokinetic properties varying among agents in the class.	Type 2 diabetes mellitus.	Low risk of hypoglycemia and neutral effect on body weight.	Mild adverse effects with rare cases of pancreatitis reported.	Dose adjustment may be required in renal impairment depending on the agent.
GLP-1 receptor agonists	Exenatide, Liraglutide, Dulaglutide	Mimic glucagon-like peptide-1, leading to glucose-dependent insulin secretion, delayed gastric emptying, and reduced appetite.	Administered by injection with varying durations of action depending on the formulation.	Type 2 diabetes mellitus and obesity management.	Promote weight loss and have a low risk of hypoglycemia.	Nausea, vomiting, and gastrointestinal discomfort.	Injectable therapy which may affect patient compliance.
SGLT-2 inhibitors	Dapagliflozin, Canagliflozin, Empagliflozin	Inhibit sodium-glucose co-transporter 2 in the renal tubules, reducing glucose reabsorption and increasing urinary glucose excretion.	Administered orally and primarily dependent on renal function for efficacy.	Type 2 diabetes mellitus.	Promote weight reduction, lower blood pressure, and provide cardiovascular benefits.	Genital infections and dehydration.	Not recommended in severe renal impairment.

Combination Therapy in Diabetes Management

The progressive nature of Type 2 diabetes mellitus often necessitates the use of combination therapy to maintain adequate glycemic control. Although lifestyle modification and monotherapy with an oral antidiabetic agent may initially be sufficient, many patients eventually require multiple medications because of progressive β-cell dysfunction and worsening insulin resistance. Combination therapy allows simultaneous targeting of multiple pathophysiological defects responsible for hyperglycemia, thereby improving therapeutic efficacy while minimizing adverse effects.

Modern diabetes management follows a patient-centered treatment approach, taking into consideration factors such as glycemic targets, risk of hypoglycemia, weight considerations, cardiovascular disease, renal function, cost, and patient preferences [49].

Rationale for Combination Therapy

Combination therapy in diabetes offers several important advantages by addressing multiple underlying mechanisms of the disease at the same time. It leads to better glycemic control while allowing the use of lower doses of individual drugs, which helps reduce the risk of adverse effects. Additionally, it contributes to the preservation of pancreatic β-cell function, thereby slowing disease progression. Compared to monotherapy, combination therapy also lowers the chances of treatment failure, making it a more effective and sustainable approach for long-term diabetes management. Combination therapy is typically considered when glycated haemoglobin (HbA1c) levels remain above target despite lifestyle modification and single-drug therapy.[50]

Table 3: Combination Therapy in Diabetes Management [51-61].

Category	Combination	Mechanism	Key Benefits	Limitations
Dual Therapy	Metformin with Sulfonylurea	Reduces hepatic glucose and increases insulin secretion	Effective glycemic control	Risk of hypoglycemia and weight gain
Dual Therapy	Metformin with DPP-4 inhibitor	Enhances incretin activity and reduces glucose production	Low hypoglycemia risk, weight neutral	Generally well tolerated
Dual Therapy	Metformin with SGLT-2 inhibitor	Increases urinary glucose excretion	Weight loss and cardiovascular benefit	Risk of urinary infections
Dual Therapy	Metformin with GLP-1 receptor agonist	Increases insulin, reduces glucagon, delays gastric emptying	Strong control and weight loss	Injectable and costly
Triple Therapy	Three-drug combinations	Targets multiple mechanisms	Improved glycemic control	Increased complexity
Insulin Combination	Basal insulin with oral drugs	Provides basal insulin support	Effective in advanced diabetes	Risk of hypoglycemia
Insulin Combination	Basal-bolus regimen	Mimics physiological insulin secretion	Tight glucose control	Complex regimen
Fixed Dose Combinations	Metformin with other agents	Combines drugs in single formulation	Improved adherence	Limited dose flexibility
Patient-Centered Approach	Individualized therapy	Based on patient factors	Optimized outcomes	Requires monitoring
Special Preference	SGLT-2 inhibitors or GLP-1 receptor agonists	Provides cardiovascular and renal benefits	Preferred in high-risk patients	Cost considerations

Adverse Effects of Antidiabetic Drugs

Table 4: Adverse Effects & Safety of Antidiabetic Drugs [62-74].

Category	Drugs	Adverse Effects	Mechanism
Hypoglycemia	Insulin, Sulfonylureas	Sweating, confusion	Excess insulin
	Metformin, DPP-4 inhibitors, SGLT-2 inhibitors	Minimal risk	Insulin-independent action
Weight	Insulin, Sulfonylureas, Thiazolidinediones	Weight gain	Increased fat storage
	GLP-1 receptor agonists, SGLT-2 inhibitors, Metformin	Weight loss	Increased satiety, glucose loss
Gastrointestinal	Metformin	Nausea, diarrhea	Dose-related
	Alpha-glucosidase inhibitors	Flatulence	Carbohydrate fermentation
Cardiovascular	Thiazolidinediones, Sulfonylureas	Heart failure risk	Fluid retention

	SGLT-2 inhibitors, GLP-1 receptor agonists	Cardioprotection	Reduced cardiovascular events
Renal	Metformin	Lactic acidosis (rare)	Accumulation in renal impairment
	SGLT-2 inhibitors	Urinary infections	Increased glucose excretion

Recent Advances in Antidiabetic Drug Therapy

Over the past two decades, significant progress has been made in the development of novel antidiabetic therapies aimed at improving glycemic control while reducing adverse effects and preventing long-term complications. Advances in molecular biology, pharmacology, and metabolic research have led to the discovery of new drug classes that target specific metabolic pathways involved in the pathogenesis of diabetes mellitus. These innovations not only improve blood glucose regulation but also offer additional benefits such as cardiovascular protection, weight reduction, and renal protection.

Recent developments in antidiabetic drug therapy include incretin-based therapies, sodium glucose cotransporter inhibitors, dual receptor agonists, ultra long-acting insulin analogues, and novel biological therapies. These advances have significantly expanded the therapeutic options available for managing diabetes [75,76].

Advanced Incretin-Based Therapies

Incretin-based therapies represent one of the most important modern approaches in diabetes treatment. These therapies exploit the physiological actions of incretin hormones, particularly glucagon-like peptide-1 (GLP-1), which enhance insulin secretion in a glucose-dependent manner.

Modern GLP-1 receptor agonists have improved pharmacokinetic properties, allowing once-daily or once-weekly administration. These drugs not only improve glycemic control but also promote weight loss and reduce cardiovascular risk. Examples of advanced GLP-1 receptor agonists including Liraglutide, Dulaglutide, Semaglutide.

These agents stimulate insulin secretion, suppress glucagon release, delay gastric emptying, and promote satiety. As a result, they improve glycemic control while reducing caloric intake and body weight [77].

Dual Incretin Receptor Agonists

A major recent advancement in diabetes pharmacotherapy is the development of dual incretin receptor agonists, which simultaneously target multiple metabolic pathways. One of the most promising agents in this class is Tirzepatide, which acts on both glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptors. Activation of these pathways enhances insulin secretion, suppresses glucagon release, improves insulin sensitivity, and promotes significant weight reduction. Clinical studies have shown that dual incretin receptor agonists produce greater reductions in HbA1c and body weight compared with traditional GLP-1 receptor agonists [78].

Next-Generation SGLT-2 Inhibitors

SGLT-2 inhibitors have gained considerable attention due to their multiple metabolic and cardiovascular benefits. Recent studies have demonstrated that these drugs not only reduce blood glucose levels but also improve outcomes in patients with cardiovascular disease and chronic kidney disease.

Examples of widely used SGLT-2 inhibitors Including Empagliflozin, Dapagliflozin, Canagliflozin.

These drugs reduce plasma glucose levels by promoting urinary glucose excretion and also provide additional benefits such as reduction in body weight, decrease in blood pressure, Protection against heart failure, Slowing progression of diabetic kidney disease. Because of these benefits, SGLT-2 inhibitors are now recommended for patients with Type 2 diabetes and established cardiovascular or renal disease [79,80].

Ultra Long-Acting Insulin Analogues

Advancements in insulin therapy have led to the development of ultra long-acting insulin analogues that provide more stable glycemic control and reduce the risk of hypoglycemia. Examples including Insulin degludec, Insulin glargine U-300. These insulin formulations have prolonged duration of action, exceeding 24 hours, which allows once-daily administration and provides more consistent basal insulin levels. Ultra long-acting insulin analogues also reduce fluctuations in blood glucose levels and decrease the incidence of nocturnal hypoglycemia [81].

Smart Insulin and Glucose-Responsive Insulin

One of the most innovative approaches in diabetes therapy is the development of glucose-responsive insulin, commonly known as “smart insulin.” This formulation is designed to release insulin only when blood glucose levels exceed a defined threshold, thereby mimicking physiological insulin regulation and minimizing the risk of hypoglycemia. Current research focuses on glucose-sensitive polymer systems, glucose-binding nanoparticles, and enzymatic glucose-responsive insulin formulations.

Although these technologies are still under investigation, they have the potential to revolutionize diabetes management in the future [82].

Gene Therapy and Stem Cell Approaches

Emerging biological therapies are exploring the possibility of restoring insulin production through gene therapy and stem cell-based approaches. Gene therapy strategies aim to introduce genes responsible for insulin production into non-β cells, enabling them to produce insulin in response to glucose. Stem cell therapy involves the differentiation of pluripotent stem cells into insulin-producing pancreatic β-cells, which may eventually be transplanted into diabetic patients. Although these approaches are still experimental, they represent promising strategies for the long-term treatment of diabetes [83].

Artificial Pancreas Systems

Technological innovations have significantly advanced diabetes management through the development of artificial pancreas systems. These systems integrate continuous glucose monitoring devices, insulin pumps, and computer algorithms that automatically adjust insulin delivery based on real-time glucose levels, thereby improving glycemic control and reducing the risk of complications. The artificial pancreas system continuously monitors blood glucose levels and delivers insulin accordingly, providing automated glycemic control and reducing the burden of diabetes management for patients [84,85].

Future Perspectives in Diabetes Treatment

Despite significant advances in the pharmacological management of diabetes mellitus, the global burden of the disease continues to increase. Current therapies primarily focus on controlling blood glucose levels and preventing complications; however, they do not completely cure the disease. Therefore, ongoing research is directed toward developing innovative therapeutic strategies that target the underlying causes of diabetes and provide long-term disease control. Future approaches in diabetes treatment involve advances in precision medicine, microbiome research, immunotherapy, regenerative medicine, and next-generation pharmacological agents. These emerging strategies aim to improve treatment outcomes, reduce complications, and potentially restore normal glucose metabolism.

Precision Medicine in Diabetes: Precision medicine represents a personalized approach to diabetes management that considers individual genetic, metabolic, and environmental factors. Unlike traditional generalized treatment strategies, it recognizes the significant variability among patients in disease progression, therapeutic response, and risk of complications. This approach aims to tailor treatment based on a patient's genetic profile, metabolic characteristics, lifestyle factors, and associated comorbid conditions, thereby improving therapeutic outcomes and safety. Advances in genomic technologies have identified several genetic variants associated with diabetes susceptibility and drug response. Understanding these genetic factors may help clinicians select the most effective antidiabetic drugs for individual patients and minimize adverse effects [86].

Microbiome-Based Therapies: Recent research has revealed a strong relationship between gut microbiota and metabolic diseases, including diabetes mellitus. The human gut microbiome plays a crucial role in regulating energy metabolism, glucose homeostasis, and inflammation. Alterations in gut microbial composition, referred to as dysbiosis, have been associated with insulin resistance and metabolic dysfunction. As a result, therapeutic strategies targeting the gut microbiome are being explored as potential approaches for diabetes management. These include probiotic supplementation, prebiotic dietary interventions, fecal microbiota transplantation, and the development of microbiome-targeted pharmaceuticals. Modulating gut microbiota may improve insulin sensitivity, reduce inflammation, and enhance glucose metabolism [87].

Immunotherapy for Diabetes: Immunotherapy is particularly relevant for Type 1 diabetes mellitus, which is an autoimmune disorder characterized by immune-mediated destruction of pancreatic β-cells. Researchers are exploring various immunomodulatory strategies to prevent or slow the autoimmune processes responsible for pancreatic β-cell destruction. These approaches include the use of monoclonal antibodies targeting specific immune cells, antigen-specific immunotherapy, and techniques aimed at inducing immune tolerance. These strategies aim to preserve residual β-cell function and delay disease progression [88].

Regenerative Medicine and Stem Cell Therapy: Regenerative medicine offers a promising approach for restoring insulin production by regenerating or replacing damaged pancreatic β-cells. Stem cell research has demonstrated the possibility of differentiating pluripotent stem cells into insulin-producing β-cells. These cells may potentially be transplanted into diabetic patients to restore endogenous insulin production. Several experimental studies have shown encouraging results in generating functional β-cells from stem cells, although challenges such as immune rejection and long-term cell survival remain to be addressed [89].

Artificial Pancreas and Closed-Loop Systems: Technological advancements have enabled the development of artificial pancreas systems, which integrate continuous glucose monitoring with automated insulin delivery to improve glycemic control. These systems consist of three key components: a continuous glucose monitoring sensor to track glucose levels, an insulin infusion pump to deliver insulin, and a control algorithm that automatically adjusts insulin dosing based on real-

time glucose data. Closed-loop systems automatically regulate insulin administration based on real-time glucose measurements, closely mimicking physiological insulin regulation. These technologies significantly improve glycemic control and reduce the risk of hypoglycemia, particularly in patients with Type 1 diabetes [90,91].

Development of Next-Generation Antidiabetic Drugs: Ongoing research is focused on identifying novel pharmacological targets involved in glucose metabolism. Several emerging therapeutic strategies are under investigation, including dual and triple incretin receptor agonists, glucagon receptor antagonists, fibroblast growth factor-21 analogues, and mitochondrial-targeted therapies. These innovative drugs aim to address multiple metabolic pathways simultaneously, providing more effective glycemic control and reducing the risk of complications [92, 93].

Conclusion

Diabetes mellitus is one of the most prevalent and challenging metabolic disorders worldwide, characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. The increasing global incidence of diabetes has created a significant burden on healthcare systems and has highlighted the urgent need for effective therapeutic strategies. Persistent hyperglycemia associated with diabetes leads to serious complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy, which significantly increase morbidity and mortality among affected individuals. Over the past several decades, substantial progress has been made in the development of pharmacological agents for the management of diabetes. A wide range of antidiabetic drugs is now available, including insulin preparations, insulin secretagogues, insulin sensitizers, incretin-based therapies, sodium–glucose cotransporter-2 inhibitors, and other novel agents. These drugs act through different mechanisms to correct metabolic abnormalities involved in the pathophysiology of diabetes and improve glycemic control. Among currently available therapies, metformin remains the first-line treatment for Type 2 diabetes mellitus due to its efficacy, safety profile, and beneficial metabolic effects. In recent years, newer drug classes such as GLP-1 receptor agonists and SGLT-2 inhibitors have gained considerable attention because of their additional benefits beyond glucose control, including weight reduction and cardiovascular protection. Combination therapy strategies have further improved treatment outcomes by targeting multiple metabolic pathways simultaneously.

In addition to conventional pharmacological therapies, advances in biotechnology and pharmaceutical sciences have introduced innovative approaches such as novel drug delivery systems, incretin-based therapies, dual receptor agonists, and ultra long-acting insulin formulations. Furthermore, emerging research in areas such as precision medicine, microbiome modulation, regenerative medicine, and artificial pancreas technologies offers promising possibilities for the future management of diabetes. Despite these advancements, diabetes remains a complex and progressive disease that requires continuous monitoring and individualized treatment strategies. Future research should focus on identifying novel therapeutic targets, improving drug safety profiles, and developing treatments that address the underlying causes of the disease rather than merely controlling blood glucose levels.

In conclusion, antidiabetic drugs play a vital role in the management of diabetes mellitus, and continued research and innovation are essential for improving therapeutic outcomes and reducing the global burden of this disease. A comprehensive understanding of the pharmacology, mechanisms of action, and clinical applications of antidiabetic agents is crucial for the development of effective treatment strategies and the advancement of diabetes care.

Conflict of Interest: none
Financial Support: none
Ethics Statement: none

References

1. (2014). American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care,* 37(S1):S81-S90.
2. Magliano DJ, Boyko EJ. (2021). IDF Diabetes Atlas 10th edition scientific committee. IDF DIABETES ATLAS [Internet]. 10th edition. Brussels: *International Diabetes Federation.*
3. Hussain A. (2025). Chronic hyperglycemia and cardiovascular dysfunction: an in-depth exploration of metabolic and cellular pathways in type 2 diabetes mellitus. Cardiovascular diabetology. *Endocrinology reports,* 11(1):39.
4. Chawla A, Chawla R, Jaggi S. (2016). Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian journal of endocrinology and metabolism,* 20(4):546-551.
5. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe, et al. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *International journal of molecular sciences*, 21(17):6275.
6. Dimitriadis G. D, Maratou E, Kountouri A, Board M, Lambadiari V. (2021). Regulation of Postabsorptive and Postprandial Glucose Metabolism by Insulin-Dependent and Insulin-Independent Mechanisms: *An Integrative Approach. Nutrients*, 13(1):159.

7. Röder P. V, Wu B, Liu Y, Han W. (2016). Pancreatic regulation of glucose homeostasis. *Experimental & molecular medicine*, 48(3):219.
8. Wilcox G. (2005). Insulin and insulin resistance. *The Clinical biochemist. Reviews*, 26(2):19-39.
9. Dludla P. V, Mabhida S. E, Ziqubu K, Nkambule B. B, Mazibuko-Mbeje S, et al. (2023). Pancreatic β-cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress. *World journal of diabetes*, 14(3):130-146.
10. Chaudhury A, Duvoor C, Reddy Dendi V. S, Kraleti S, Chada A, et al. (2017). Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. *Frontiers in endocrinology*, 8:6.
11. Donnor T, Sarkar S. Feingold KR, Adler RA, Ahmed SF, et al. (2023). Insulin- Pharmacology, Therapeutic Regimens and Principles of Intensive Insulin Therapy. [Updated 2023 Feb 15]. In: editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, *Inc.*
12. Hartman I. (2008). Insulin analogues: impact on treatment success, satisfaction, quality of life, and adherence. *Clinical medicine & research,* 6(2):54-67.
13. Munguia C, Correa R. (2026). Regular Insulin. [Updated 2023 Jul 3]. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing.*
14. Saleem F, Sharma A. NPH Insulin. (2026). [Updated 2023 Jun 12]. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing.*
15. Tiwari D. D, Thorat V. M, Pakale D. P. V. (2024). Newer Insulin Preparations and Insulin Analogues876. *Cureus*, 16(11):74593.
16. Wang F, Surh J, Kaur M. (2012). Insulin degludec as an ultralong-acting basal insulin once a day: a systematic review. Diabetes, metabolic syndrome and obesity: targets and therapy, 5:191-204.
17. Li X. T, Yun M. Z. (2025). The impact of sulfonylureas on diverse ion channels: an alternative explanation for the antidiabetic actions. *Frontiers in cell and developmental biology*, 13:1528369.
18. Hemmingsen B, Sonne D. P, Mittendorf M. I, Richter B. (2016). Insulin secretagogues for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus. The Cochrane database of systematic reviews, 10(10):CD012151
19. Top W. M. C, Kooy A, Stehouwer C. D. A. (2022). Metformin: A Narrative Review of Its Potential Benefits for Cardiovascular Disease, Cancer and Dementia. *Pharmaceuticals (Basel, Switzerland),* 15(3):312.
20. Eggleton JS, Jiali I. (2026). Thiazolidinediones. [Updated 2023 Feb 20]. In: StatPearls [Internet]. Treasure Island (FL). *StatPearls Publication.*
21. Akmal M, Patel P, Wadhwa R. (2026). Alpha Glucosidase Inhibitors. [Updated 2024 Feb 28]. In: StatPearls [Internet]. Treasure Island (FL). *StatPearls.*
22. Nauck M. A, Meier J. J. (2018). Incretin hormones: Their role in health and disease. *Diabetes, obesity & metabolism*, 20(1):5-21.
23. Kasina SVSK, Baradhi KM. (2026). Dipeptidyl Peptidase IV (DPP IV) Inhibitors. [Updated 2023 May 22]. In: *StatPearls [Internet]. Treasure Island (FL).*
24. Collins L, Costello RA. (2026). Glucagon-Like Peptide-1 Receptor Agonists. [Updated 2024 Feb 29]. In: *StatPearls [Internet]. Treasure Island (FL).*
25. Padda IS, Mahtani AU, Parmar M. (2026). Sodium-Glucose Transport 2 (SGLT2) Inhibitors. [Updated 2025 Sep 15]. In: *StatPearls [Internet]. Treasure Island (FL).*
26. Hoogwerf B. J, Doshi K. B, Diab D. (2008). Pramlintide, the synthetic analogue of amylin: physiology, pathophysiology, and effects on glycemic control, body weight, and selected biomarkers of vascular risk. *Vascular health and risk management*, 4(2):355-362.
27. Yang T, Wang H, Li C, Duan H. (2023). Mechanisms of drugs in the treatment of type 2 diabetes mellitus. *Chinese medical journal*, 136(4):394-396.
28. De Meyts P, Feingold KR, Adler RA, Ahmed SF. et al. (2000). The Insulin Receptor and Its Signal Transduction Network. [Updated 2016 Apr 27]. In: editors. Endotext [Internet]. South Dartmouth (MA): *MDText.com.*
29. Fontana F, Giannitti G, Marchesi S, Limonta P. (2024). The PI3K/Akt Pathway and Glucose Metabolism: A Dangerous Liaison in Cancer. *International journal of biological sciences*, 20(8):3113-3125.
30. G. Y. Q, Loh Z. W, Fann D. Y, Mallilankaraman K, Arumugam T. V, Hande M. P. (2024). Role of Mitogen-Activated Protein (MAP) Kinase Pathways in Metabolic Diseases. *Genome integrity*, 15:20230003.
31. Ashcroft F. M. (2005). ATP-sensitive potassium channelopathies: focus on insulin secretion. The *Journal of clinical investigation*, 115(8):2047-2058.
32. Stephenne X, Foretz M, Taleux N, van der Zon G. C, Sokal E, et al. (2011). Metformin activates AMP-activated protein kinase in primary human hepatocytes by decreasing cellular energy status. *Diabetologia,* 54(12):3101-3110

33. Hunter R. W, Hughey C. C, Lantier L, Sundelin E. I, Peggie M, et al. (2018). Metformin reduces liver glucose production by inhibition of fructose-1-6-bisphosphatase. *Nature medicine*, 24(9):1395-1406.
34. Wei X. L, Tao M. H, Li R. H, Ge S. H, Xiao W. (2025). Metformin and Adipose Tissue: A Multifaceted Regulator in Metabolism, Inflammation, and Regeneration. *Endocrinology and metabolism (Seoul, Korea)*, 40(4):523-538.
35. Chiarelli, F, Di Marzio D. (2008). Peroxisome proliferator-activated receptor-gamma agonists and diabetes: current evidence and future perspectives. *Vascular health and risk management*, 4(2) 297-304.
36. Gilbert M. P, Pratley R. E. (2020). GLP-1 Analogues and DPP-4 Inhibitors in Type 2 Diabetes Therapy: Review of Head-to-Head Clinical Trials. *Frontiers in endocrinology*, 11:178.
37. Liu Q. K. (2024). Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. *Frontiers in endocrinology*, 15:1431292.
38. Abdul-Ghani M. A, Norton L, DeFronzo R. A. (2015). Renal sodium-glucose cotransporter inhibition in the management of type 2 diabetes mellitus. *American journal of physiology. Renal physiology*, 309(11):F889-F900.
39. Castellana E, Budau P. M, Chiappetta M. R. (2026). Overview of Diabetes Medications: Traditional and New-Generation Agents and Their Off-Label Use for Weight Loss. jPT: official publication of the Association of Pharmacy Technicians, *The Journal of pharmacy technology* 87551225261422610.
40. Dutta S, Shah R. B, Singhal S, Dutta S. B, Bansal S, et al. (2023). Metformin: A Review of Potential Mechanism and Therapeutic Utility Beyond Diabetes. Drug design, development and therapy, 17:1907-1932.
41. Hundal R. S, Krssak M, Dufour S, Laurent D, Lebon V. (2000). Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes,* 49(12):2063-2069.
42. Gong L, Goswami S, Giacomini K. M, Altman R. B, & Klein T. E. (2012). Metformin pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenetics and genomics*, 22(11): 820-827.
43. Costello RA, Nicolas S, Shivkumar A. Sulfonylureas. (2026). [Updated 2023 Jul 12]. In: *StatPearls [Internet]. Treasure Island (FL).*
44. Sola D, Rossi L, Schianca G. P, Maffioli P, Bigliocca M. (2015). Sulfonylureas and their use in clinical practice. *Archives of medical science* AMS, 11(4):840-848.
45. Proks P, Reimann F, Green N, Gribble F, Ashcroft, F. (2002). Sulfonylurea stimulation of insulin secretion. *Diabetes*, 51(3):S368-S376
46. Pakkir Maideen N. M, Manavalan G, Balasubramanian K. (2018). Drug interactions of meglitinide antidiabetics involving CYP enzymes and OATP1B1 transporter. *Therapeutic advances in endocrinology and metabolism*, 9(8):259-268.
47. Quinn C. E, Hamilton P. K, Lockhart C. J, McVeigh, G. E. (2008). Thiazolidinediones: effects on insulin resistance and the cardiovascular system. *British journal of pharmacology*, 153(4):636-645.
48. Vasquez-Rios G, Nadkarni, G. N. (2020). SGLT2 Inhibitors: Emerging Roles in the Protection Against Cardiovascular and Kidney Disease Among Diabetic Patients. *International journal of nephrology and renovascular disease,* 13:281-296.
49. Kim J. Y, Kim N. H. (2024). Initial Combination Therapy in Type 2 Diabetes. *Endocrinology and metabolism (Seoul, Korea)*, 39(1):23-32.
50. Xie X, Wu C, Hao Y, Wang T, Yang Y, et al. (2023). Benefits and risks of drug combination therapy for diabetes mellitus and its complications: a comprehensive review. *Frontiers in endocrinology*, 14:1301093.
51. Singh A. K, Singh R, Chakraborty P. P. (2021). Diabetes Monotherapies versus Metformin-Based Combination Therapy for the Treatment of Type 2 Diabetes. *International journal of general medicine,* 14:3833-3848.
52. Madsen K. S, Kähler P, Kähler L. K, Madsbad S, Metzendorf M, et al. (2016). Metformin and sulphonylurea (second- or third-generation) combination therapy for adults with type 2 diabetes mellitus. *The Cochrane Database of Systematic Reviews*, 2016(9):CD012368.
53. Chen R, Li J, Chen D, Wen W, Zhang S, et al. (2024). Efficacy and Safety of DPP-4 Inhibitors and Metformin Combinations in Type 2 Diabetes: A Systematic Literature Review and Network Meta-Analysis. *Diabetes, metabolic syndrome and obesity: targets and therapy*, 17:2471-2493.
54. Wilcox T, De Block C, Schwartzbard A. Z, Newman J. D. (2020). Diabetic Agents, From Metformin to SGLT2 Inhibitors and GLP1 Receptor Agonists: JACC Focus Seminar. *Journal of the American College of Cardiology,* 75(16):1956-1974.
55. Olukorode J. O, Orimoloye D. A, Nwachukwu N. O, Onwuzo C. N, Oloyede P. O, et al. (2024). Recent Advances and Therapeutic Benefits of Glucagon-Like Peptide-1 (GLP-1) Agonists in the Management of Type 2 Diabetes and Associated Metabolic Disorders. *Cureus,* 16(10): e72080.
56. Yu M, Wang T, Xu C, Bi Y, Gao L, et al. (2025). Steering Committee, Development Group, & Diabetes Committee of the Chinese Research Hospital Association Triple oral therapy with metformin, DPP-4 inhibitor, and SGLT2 inhibitor for adults with type 2 diabetes: Consensus recommendations of a Chinese expert panel (version 2025). *Diabetes, obesity & metabolism,* 279:3-17.

57. Hermansen K, Mortensen L. S, Hermansen M. L. (2008). Combining insulins with oral antidiabetic agents: effect on hyperglycemic control, markers of cardiovascular risk and disease. *Vascular health and risk management*, 4(3):561-574.
58. Wollenhaupt D, Wolters J, Abd El Aziz, M, Nauck M. A. (2023). Impact of concomitant oral glucose-lowering medications on the success of basal insulin titration in insulin-naïve patients with type 2 diabetes: a systematic analysis. *BMJ open diabetes research & care,* 11(4):e003296.
59. Vidovic J, Hirsch IB. Feingold KR, Adler RA, Ahmed SF, et al. (2000) Initial Management of Severe Hyperglycemia in Type 2 Diabetes. [Updated 2026 Jan 12]. In Endotext [Internet]. South Dartmouth (MA).
60. Kalra S, Das A. K, Priya G, Ghosh S, Mehrotra, R. N, et al. (2020). Fixed-dose combination in management of type 2 diabetes mellitus: Expert opinion from an international panel. *Journal of family medicine and primary care*, 9(11):5450-5457.
61. Quattrocchi E, Goldberg T, Marzella N. (2020). Management of type 2 diabetes: consensus of diabetes organizations. Drugs in context, 9: 212607.
62. Huri H. Z, Ling D. Y, Ahmad W. A. (2015). Association between glycemic control and antidiabetic drugs in type 2 diabetes mellitus patients with cardiovascular complications. Drug design, development and therapy, 9:4735-4749.
63. Mathew P, Thoppil D. Hypoglycemia. (2026) [Updated 2022 Dec 26]. In: StatPearls [Internet]. Treasure Island (FL).
64. Apovian C. M, Okemah J, O'Neil P. M. (2019). Body Weight Considerations in the Management of Type 2 Diabetes. *Advances in therapy*, 36(1):44-58.
65. Kalra S, Kalra B, Unnikrishnan A, Agrawal N, Kumar S. (2010). Optimizing weight control in diabetes: antidiabetic drug selection. Diabetes, metabolic syndrome and obesity: targets and therapy, 3:297-299.
66. Haddad F, Dokmak G, Bader M, Karaman R. (2023). A Comprehensive Review on Weight Loss Associated with Anti-Diabetic Medications. Life (Basel, Switzerland), 13(4):1012.
67. Siavash M, Tabbakhian M, Sabzghabaee A. M, Razavi, N. (2017). Severity of Gastrointestinal Side Effects of Metformin Tablet Compared to Metformin Capsule in Type 2 Diabetes Mellitus Patients. *Journal of research in pharmacy practice*, 6(2):73-76.
68. Kumar R, Kerins D. M, Walther T. (2016). Cardiovascular safety of anti-diabetic drugs. *European heart journal. Cardiovascular pharmacotherapy*, 2(1):32-43.
69. Brown J. M, Everett B. M. (2019). Cardioprotective diabetes drugs: what cardiologists need to know. *Cardiovascular endocrinology & metabolism,* 8(4):96-105.
70. Betônico C. C, Titan S. M, Correa-Giannella M. L, Nery M, et al. (2016). Management of diabetes mellitus in individuals with chronic kidney disease: therapeutic perspectives and glycemic control. *Clinics (Sao Paulo, Brazil),* 71(1):47-53.
71. Kessler L. E, Sachdeva D, Singhal R, Wortman Ii K. O, Lall R. (2025). Metformin-Associated Lactic Acidosis (MALA): When a Common Drug Turns Catastrophic. *Cureus,* 17(8):e89292.
72. Dai Z. C, Chen J. X, Zou R, Liang X. B, Tang J. X, et al. (2023). Role and mechanisms of SGLT-2 inhibitors in the treatment of diabetic kidney disease. *Frontiers in immunology,* 14:1213473.
73. May M, Schindler, C. (2016). Clinically and pharmacologically relevant interactions of antidiabetic drugs. *Therapeutic advances in endocrinology and metabolism,* 7(2):69-83.
74. Alwafi H, Wong I. C. K, Naser A. Y, Banerjee A, Mongkhon P, et al. (2022). Concurrent Use of Oral Anticoagulants and Sulfonylureas in Individuals with Type 2 Diabetes and Risk of Hypoglycemia: A UK Population-Based Cohort Study. *Frontiers in medicine*, 9:893080.
75. Dahlén A. D, Dashi G, Maslov I, Attwood M. M, Jonsson J, et al. (2022). Trends in Antidiabetic Drug Discovery: FDA Approved Drugs, New Drugs in Clinical Trials and Global Sales. *Frontiers in pharmacology*, 12:807548.
76. Chatzianagnostou K, Gaggini M, Suman Florentin A, Simonini, L, Vassalle C. (2024). New Molecules in Type 2 Diabetes: Advancements, Challenges and Future Directions. International *Journal of Molecular Sciences*, 25(11): 6218.
77. Zarei M, Sahebi Vaighan N, Farjoo M. H, Talebi S, Zarei M. (2024). Incretin-based therapy: a new horizon in diabetes management. *Journal of diabetes and metabolic disorders*, 23(2):1665-1686.
78. Tan Q, Akindehin S. E, Orsso C. E, Waldner R. C, DiMarchi R. D, et al. (2022). Recent Advances in Incretin-Based Pharmacotherapies for the Treatment of Obesity and Diabetes. *Frontiers in endocrinology*, 13:838410.
79. Movila D, Seiman D. D, Dragan S. R. (2025). Next-Generation SGLT2 Inhibitors: Innovations and Clinical Perspectives. *Biomedicines,* 14(1):81.
80. Stielow M, Fijałkowski Ł, Alaburda A, Grześk G, Grześk E, et al. (2025). SGLT2 Inhibitors: From Molecular Mechanisms to Clinical Outcomes in Cardiology and Diabetology. *Molecules,* 30(15):3112.
81. Sibiya N, Dzimwasha L, Zvandasara S, Zuma A, Khathi A. (2025). Emerging Insulin Analogues: A Glimpse into How Insulin Analogues May Look in the near Future. *Pharmaceutics,* 17(10):1239.

82. Rege N. K, Phillips N. F. B, Weiss M. A. (2017). Development of glucose-responsive 'smart' insulin systems. Current opinion in endocrinology, diabetes, and obesity, 24(4):267-278.
83. Khartabil N, Avoundjian A. (2025). Gene Therapy and Diabetes: A Narrative Review of Recent Advances and the Role of Multidisciplinary Healthcare Teams. *Genes,* 16(1):107.
84. Kitagawa H, Munekage M, Seo S, Hanazaki K. (2025). Artificial pancreas: the past and the future. *Journal of artificial organs: the official journal of the Japanese Society for Artificial Organs,* 28(4):514-521.
85. Klonoff D. C, Zimliki C. L, Stevens L. A, Beaston P, Pinkos A, et al. (2011). Innovations in technology for the treatment of diabetes: clinical development of the artificial pancreas (an autonomous system). *Journal of diabetes science and technology,* 5(3):804-826.
86. Chung W. K, Erion K, Florez J. C, Hattersley A. T, Hivert M. F, et al. (2020). Precision Medicine in Diabetes: A Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes care,* 43(7):1617-1635.
87. Alqahtani M. S. (2025). The Gut Microbiota-Metabolic Axis: Emerging Insights from Human and Experimental Studies on Type 2 Diabetes Mellitus-A Narrative Review. *Medicina (Kaunas, Lithuania),* 61(11).
88. Chen W, Xie A, & Chan L. (2013). Mechanistic basis of immunotherapies for type 1 diabetes mellitus. *Translational research: the journal of laboratory and clinical medicine,* 161(4):217-229.
89. Kumar D, Tanwar R, Gupta V. (2025). First-ever stem cell therapy restores insulin independence in type 1 diabetes: A medical milestone. *World journal of stem cells,* 17(7):106856.
90. Lal R. A, Ekhlaspour L, Hood K, Buckingham B. (2019). Realizing a Closed-Loop (Artificial Pancreas) System for the Treatment of Type 1 Diabetes. *Endocrine reviews,* 40(6):1521-1546.
91. Templer S. (2022). Closed-Loop Insulin Delivery Systems: Past, Present, and Future Directions. *Frontiers in endocrinology,* 13:919942.
92. Gutgesell R. M, Nogueiras R, Tschöp M. H, Müller T. D. (2024). Dual and Triple Incretin-Based Co-agonists: Novel Therapeutics for Obesity and Diabetes. Diabetes therapy: research, treatment and education of diabetes and related disorders, 15(5):1069-1084.
93. Bailey C. J. (2026). Pharmacological therapies for type 2 diabetes: future approaches. *Diabetologia,* 69(1):20-35.