©IDOSR PUBLICATIONS International Digital Organization for Scientific Research

IDOSR JOURNAL OF SCIENTIFIC RESEARCH 11(1):131-138, 2026. ISSN: 2550-794X

https://doi.org/10.59298/IDOSRJSR/2026/11.1.131138 IDOSRJSR11106

Novel Pharmacotherapies for Type 2 Diabetes

Kintuza Lumwako Tebulo

Faculty of Medicine Kampala International University Uganda

ABSTRACT

Over the past five years, the therapeutic landscape of type 2 diabetes mellitus (T2DM) has expanded with the emergence of novel pharmacotherapies targeting diverse pathophysiological pathways. These agents, including incretin-based therapies, dual and triple receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, hepatokine modulators, and islet-targeted strategies, allow for individualized treatment approaches aimed at improving glycemic control, mitigating cardiovascular and renal risks, and addressing obesity-related complications. Advances in pharmacodynamics, pharmacokinetics, and biomarker-guided therapy facilitate personalized medicine, while combination therapies and fixed-dose regimens enhance efficacy and adherence. Clinical trial data support the safety and cardiometabolic benefits of these agents across diverse populations. Implementation in clinical practice requires careful patient selection, dose optimization, and monitoring, particularly in special populations with comorbidities. Overall, these novel pharmacotherapies provide promising tools to improve metabolic outcomes, delay disease progression, and reduce long-term complications in patients with T2DM.

Keywords: Type 2 diabetes mellitus, Incretin-based therapy, SGLT2 inhibitors, GLP-1/GIP dual agonists, and personalized pharmacotherapy.

INTRODUCTION

Over the last five years, the therapeutic landscape of type 2 diabetes has evolved substantially as new pharmacologic agents have emerged. These novel treatments, which act on distinct mechanistic pathways, provide clinicians with the ability to tailor regimens to individual patients and target remaining pathophysiologic abnormalities [2]. Effective agent selection increases the likelihood of glycemic control and reduces the potential for long-term micro- and macrovascular complications [1]. Overweight and obesity exacerbate these pathologic processes; therefore, simultaneous pharmacologic intervention targeting the underlying cause of diabetes represents an important treatment goal [2]. Emerging agents enhance therapeutic options to overcome treatment barriers associated with established therapies. Dipeptidyl peptidase-4 (DPP-4) inhibitors, the first-line adjunct to metformin, exhibit neutral effects on body weight and a low potential for hypoglycemia; combinations with other agents, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors, are common [3]. The initiation of insulin therapy remains a formidable challenge. For individuals requiring insulin, glucagon-like peptide-1 (GLP-1) receptor agonists offer the advantage of modest weight loss, improved satisfaction with therapy, and decreased glucose variability [5].

Background on Type 2 Diabetes Pathophysiology and Current Therapeutics

Diabetes mellitus is characterized by chronic hyperglycemia resulting from insufficient insulin production, impaired insulin action (insulin resistance), or both [2]. Type 2 diabetes mellitus (T2DM) is the most prevalent form and accounts for more than 90% of the estimated 537 million adults living with diabetes worldwide [4]. The development of T2DM typically follows an insidious yet progressive course. Initially, insulin resistance occurs primarily in skeletal muscle, liver, and adipose tissue with associated compensatory mechanisms leading to increased insulin secretion from pancreatic β-cells and yet normal or only mildly impaired glucose levels[1]. Non-pharmacological interventions remain the first therapeutic strategy to prevent or delay the onset of overt

hyperglycemia, an abnormality that is observed in the clinical setting before the disease is detectable. The overall objective of this article is to focus on the new drugs currently in development for T2DM patients [5].

Emerging Pharmacotherapies

Several new pharmacotherapeutic agents have arrived for managing type 2 diabetes (T2D) and have emerged in familial fits such as incretin-based agents, metabolite modulators, peptide-based hormones, and orally-delivered drugs [4]. Dipeptidyl peptidase (DPP)-4 inhibitors and glucagon-like peptide (GLP)-1 receptor agonists face more critical scrutiny than other treatment modalities as they exert their actions through the incretin route[4]. Their positions are further confined by the advent of new dual-acting and triple-acting incretin formulations, such as glycaemic control agents targeting interactions to agonist pockets of the GLP-1 receptor [5]. Further efforts are being made to replace GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) through oral delivery of suitable agents modulating endogenous surfaces of the two incretin peptides, with the hope that extended metabolic control will follow [3]. Other prominent agent types include SGLT2 inhibitors, a class with the longest clinical exposures and established cardiovascular benefits. Sodium-glucose transport across the nephron SGLT2 appears fully occupied at moderate elevations of glycaemia (>12 mmol/l), and hypovolaemia can be corrected through nephron SGLT1. Hence, HbA1c may be lowered less in severely hyperglycaemic T2D cases [6]. Inadequate SGLT2 blockade can exploit components of the insulin resistance pathway [8]. Then, innovative SGLT2 agents have been identified alongside the ongoing momentum towards protective broad-spectrum non-insulin strategies and flexible combinations partnered with GLP-1, DPP-4, metformin, and potentially other existing drugs [8].

Incretin-Based Therapies beyond GLP-1 Receptor Agonists

In patients with type 2 diabetes mellitus (T2DM), incretin-based therapies are represented by GLP-1 receptor agonists and DPP-4 inhibitors [5]. Incretin hormones released in response to food intake are critical for glucose-dependent insulin, glucagon, and somatostatin secretion [6]. GLP-1 has additional cardioprotective, neuroprotective, and anti-inflammatory effects via activation of GLP-1 receptors in the myocardial tissue and the central nervous system. Although the physiological role of GIP remains ambiguous, many people with T2DM exhibit impaired GIP-induced insulin secretion [7]. Native incretins are rapidly inactivated by DPP-4, necessitating continuous infusion in pharmacotherapy. To overcome these limitations, therapeutic agents targeting incretins include synthetic, degradation-resistant peptides that mimic GLP-1 (GLP-1R agonists) and DPP-4 inhibitors that prolong endogenous incretin activity [5]. Available GLP-1R agonists include exenatide, liraglutide, and albiglutide; DPP-4 inhibitors include sitagliptin, vildagliptin, saxagliptin, and alogliptin [7]. Phase III clinical trials have established the anti-hyperglycemic efficacy of these classes as monotherapy and in combination with metformin, thiazolidinedione, or sulfonylurea. All agents decrease glycosylated hemoglobin (A1C) levels and fasting and postprandial blood glucose concentrations. Important, nearly all agents promote dose-dependent, sustained weight loss [8].

Dual and Triple Agonists Targeting Metabolic Hormone Pathways

The cyclic, endogenous, 22-amino-acid peptide GLP-1(7-36) amide mimics the action of incretin, a hormone released in response to nutrient ingestion that stimulates physiological insulin secretion [8]. It plays a central role in oral glucose metabolism, induces pancreatic beta-cell proliferation and neogenesis, regulates glucagon secretion from pancreatic alpha-cells, promotes gastric emptying, participates in taste perception mechanisms and energy homeostasis regulation, and shows stimulating effects on the central nervous system [1]. Yet the therapeutic applicability of GLP-1 receptor (GLP-1R) activation could be constrained by more than 90% of patients remaining inadequately controlled after mono-therapy [2]. Therefore, co-activation of the glucose-dependent insulinotropic polypeptide receptor (GIPR) represents an attractive approach [3]. Although historically the glucose-dependent insulinotropic polypeptide (GIP) hormone, secreted in response to oral nutrient exposure, was considered ineffective for treatment of type 2 diabetes (T2D), activation of GIPR by monotherapy or dual agonist strategy was subsequently shown to enhance glucose-dependent insulin secretion from pancreatic beta-cells, exert anti-apoptotic and pro-survival effects on beta-cells, ameliorate lipid metabolism, improve ectopic fat redistribution, and protect against fatty liver[10]. Several dual GIPR–GLP-1R agonists (such as cotadutide, twincretin, K116, and DA-159) demonstrating enhanced glucose-altering actions, improved mechanisms of action, and complementary weight impact have shown promise in preclinical and clinical development. Collectively, consonance at the beta-cell, hepatic, adipose, and central levels supports the emerging role of GIP incretin in T2D management [9].

SGLT2 Inhibitors with Innovative Mechanisms

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) are a new class of oral antihyperglycemic agents for adults with type 2 diabetes (T2D). SGLT2 is primarily expressed in the proximal tubule of the kidney, where it plays a major role in glucose reabsorption [13]. Inhibition of SGLT2 facilitates urinary glucose excretion and lowers blood glucose levels. Unlike conventional antihyperglycemic agents, SGLT2is promote significant weight loss and have favorable effects on cardiovascular (CV) and renal outcomes independent of glucose-lowering effects.

Dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, and luseogliflozin have been approved in various countries for the treatment of patients with T2D [10]. The first-generation SGLT2is act selectively on SGLT2 [3]. Dual SGLT1/SGLT2 inhibitors, such as sotagliflozin, can also reduce tubular glucose reabsorption and improve glycemic control in T2DM. Sotagliflozin inhibits renal SGLT2, principally responsible for glucose reabsorption, leading to glucosuria similar to selective SGLT2 inhibitors [21]. It additionally increases circulating levels of the incretins GLP-1 and PYY, which potentiate glucose-induced insulin release and suppress appetite. Combining sotagliflozin with DPP-4 inhibitors, such as sitagliptin, has shown synergistic effects and enhanced glucose-induced GLP-1 release [23].

Hepatokine-Modulating Agents

Hepatokine-modulating agents comprise a class of drugs that target the liver by modulating hepatic secretion of glucose and lipids or by affecting the circulating concentration of hepatokines. Among existing pharmacotherapies, pioglitazone and some sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin and dapagliflozin, facilitate their action via the liver [11]. Agents currently under investigation include saroglitazar (as a single agent) and lanifibranor (as add-on therapy) [10]. Saroglitazar, a PPAR α/γ dual agonist, regulates hepatic lipid metabolism, improving insulin sensitivity and reducing hepatic lipid accumulation [12]. It is the first drug approved in India for treating diabetic dyslipidemia. It also lowers liver enzymes in type 2 diabetes patients with nonalcoholic fatty liver disease (NAFLD) 12. Lanifibranor is a pan-PPAR agonist that influences lipid and glucose homeostasis. The drug has been shown to reduce liver fat and improve liver injury in patients with type 2 diabetes and NAFLD [13].

Islet-Targeted and Beta-Cell Protective Strategies

The loss of β-cell mass and function that occurs in type 2 diabetes (T2D) is the most important pathophysiologic defect of the disease, driving progression of glucose homeostasis dysregulation from the initial insulin resistance to the later overt hyperglycemia[13]. Therefore, maintenance or restoration of β-cell mass and/or function remains at the forefront of research to achieve durable improvements in glycemia [14]. A number of islet-targeted and β-cell protection strategies have been developed that increase the glucose-dependent insulin secretory responses, enhance the β-cell resistance to deterioration, and/or stimulate the potential regenerative capacity of the residual β-cells 13. Since GLP-1 receptor agonist is already covered in another section, only the agents with mechanisms of action that have not been addressed previously will be appended in this section[12]. Isolated human islets or primary human β-cells cultured under either non-diabetic or diabetic conditions have been treated with a large number of agents to promote β-cell protection and regeneration and to examine their mechanism of action at either transcriptomic or proteomic levels [14].

Combination Therapies and Fixed-Dose Regimens

Pathways of glucose metabolism, incretin function, action of insulin and glucagon, and other physiological loops constitute the central basis of the accumulation of diabetes pathogenic mechanisms that should be targeted in combination therapies [11]. Current first-line choices, such as the biguanide metformin or any one of the three classes of the glucagon-like peptide 1 receptor agonists, either a threshold-triggered glucose-dependent insulin secretagogue, or a sodium-glucose cotransporter-two inhibitor, are not themselves curative but knowably preclude premature progression to the irreversible fasting or basal glucose excursions characteristic of advanced and end-stage type two diabetes [15]. Moreover, combination therapies are available in fixed-dose presentations through the incorporation of an antihypertensive agent into other antihyperglycemics [16]. By acting additively through distinct mechanisms of action, targeted combination therapies can prevent or delay progression and/or help maintain mean A1C within the center of the goal by engineering modifications of glucose balance without undue risk of hypoglycemia [18].

Mechanistic Insights and Translational Considerations

A recent analysis synthesizes the mechanisms of pharmacological treatments for type 2 diabetes, based on preliminary clinical evidence [6]. Type 2 diabetes is initiated by hepatic insulin resistance and agonist-induced inflammation, which triggers dysregulation of specific liver genes. Also, the myokine GDF15 augments this signalling pathway [5]. The drug PPARβ/δ protects against insulin resistance and inflammatory responses and ameliorates cardiovascular complications independently of glucose homeostasis, enhancing its potential utility [7]. Diabetes-induced cardiac remodelling and alterations in cardiac metabolism are inextricably linked [9]. The glucocorticoid receptor promotes diabetes-induced transdifferentiation of atrial cardiomyocytes into fibrotic fibroblasts and reduces insulin signalling in cardiomyocytes. Glucocorticoid receptor modulators restore insulin signalling and block cardiac remodeling [7]. The hepatokine FGF21, a key component of the UCP1-independent pathway associated with chronic hyperglycaemia, has a role in cardiac remodelling. FGF21 diminishes interstitial fibrosis in diabetic hearts via Akt/forkhead cell-fat transcription factor 1/enzymatic pathways. Administration of liver-targeted FGF21 alleviates cardiac stress without altering glycaemia [8]. Agonists of GHS-R1a in the

hypothalamus stimulate energy expenditure and attenuate hyperglycaemia. This approach is unfeasible in diabetes, since GHS-R1a signalling becomes upregulated in the early stages, only to subsequently decline. GHS-R1a is negatively regulated by Smad3. Mutually antagonistic circuits control agouti-related peptide and proopiomelanocortin neurons. SMAD3 antagonists, FGF21, and FGF19 act at liver neural circuits, leading to an upstream restoration of GHS-R1a activity. FGF21 boosts GHS-R1a activity, whereas FGF19 enhances overall metabolic action across tissues [6]. Metformin initially promotes increased energy expenditure, which is subsequently lost in the course of diabetic progression. FGF21 and FGF19 re-establish the action lost in type 2 diabetes [4]. Tripeptide-L and the gut microbiota-derived metabolite indole-3-propionic acid stimulate energy metabolism through distinct mechanisms. Tripeptide-L downregulates PTTG1, while indole 3-propionic-acid upregulates GFRAL pathway components [8].

Pharmacodynamics and Pharmacokinetics in Diverse Populations

Novel pharmacotherapies targeting the incretin axis, metabolic hormone pathways, the kidneys, hepatokines, and pancreatic islets are emerging as important complementary treatment options for T2D [3]. A key shift toward mechanistic characterizations of early-phase clinical data for these agents may extend their applicability beyond the traditional population to individuals classified in alternative phenotypes within T2D; provide insights into the potential for combinatorial regimens with T2D medications already in use, and articulate mechanisms of response variation [5]. Characterizing pharmacodynamics (PD) and pharmacokinetics (PK) differences across ethnicities, sex, lifestyle factors, and genetic backgrounds may further enhance both personalized recommendations and translational understanding [17]. The rising incidence of obesity, a major risk factor for T2D, among children, adolescents, and young adults is creating a need for a more integrated understanding of the disease process and, by extension, of how current and novel therapies can improve outcomes [5]. With fundamentally different profiles from glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor (GLP-1R) agonists and with a dual agonism claim supported by change-of-function modeling studies, the GLP-1/GIP co-agonist tirzepatide presents an opportunity for a broader evaluation of the mechanistic basis underlying the observed glycemic and weight-lowering effects across multiple populations [18].

Biomarkers for Response and Safety

Measurements of biomarkers associated with the safety and efficacy of pharmacotherapies for type 2 diabetes (T2D) can inform individual and subpopulation responses to therapy [3]. Insulin-response markers will indicate whether adjunctive medications targeting β-cell function will be beneficial to a therapeutic regimen. Several studies have identified genetic and metabolic biomarkers associated with the efficacy of specific glucose-lowering agents in T2D[5]. Pharmacometabolomics, a rapidly evolving field, examines treatment-induced perturbations in endogenous metabolites that can directly or indirectly indicate drug action. Mesopotamian studies show that significant metabolic alterations follow administration of metformin and other T2D therapies, and that analysis of specific metabolites may thus provide biomarkers of response and safety [19]. Substantial inter-individual heterogeneity exists in drug responses, but even among patients with similar drug-response phenotypes, subsequent treatment with the same drug results in differential metabolic responses [13]. A recent analysis of 1,738 plasma metabolites revealed that ~770 were affected by metformin, and that subgroup-specific pharmacometabolomic signatures could be identified and linked to the mechanisms of action and targets of concomitant glucose-lowering therapies [15]. Such signatures comprise additional modalities of guidance for the selection of agents in polytherapy. Ultimately, consideration of treatment-associated metabolic variations and the regulatory framework governing their study may inform strategy, enhancing the identification and validation of suitable metabolic biomarkers [16]. Further insights on the association of pharmacogenetic markers with the action of glucose-lowering medications of specific classes have emerged from the analysis of large multi-ethnic discovery cohorts combined with T2D-targeted genotyping in diverse individuals. Differences in both genetic variants and clinical features exist between individuals of European versus non-European ancestry, underscoring the need to characterize population-specific variations in genetic determinants of drug response before clinical application [17]. Examples of variants affecting pharmacological responses in T2D include those in KCNJ11, UGT1A6, SLC30A8, and GIPR, all shared with related studies. Preclinical investigations indicate that genes such as INSR, GLP1R, RBP4, and GCKR may further influence glucose-lowering responses to various drug classes [18].

Safety Profiles, Tolerability, and Cardiometabolic Outcomes

Of the six emerging classes of pharmacotherapy that directly address type 2 diabetes-related pathophysiology, two in particular have been highlighted as being closely affiliated with cardiometabolic disease and therefore warranting specific attention to their safety profiles [13]. Incretin-based therapies beyond GLP-1 receptor agonists, including GIP receptor agonists (a mechanism already elaborated) and DPP-4 inhibitors, have been associated with serious adverse events following glucagon receptor-mediated diazoxide-like effects [15]. However, these therapy classes have nevertheless been investigated within cardiovascular outcome trials and have

demonstrated a near-zero excess risk of major adverse cardiovascular events across diverse clinical settings [20]. Similarly, although sodium-glucose cotransporter-2 inhibitors with innovative mechanisms (another class already detailed) exert the cardiometabolically beneficial effect of heart failure prevention, they have shown the ability to protect against elevated heart rate and cardiac stress and displayed protective effects against heart failure across diverse trial populations [21]. The safety profiles, tolerability, and cardiometabolic outcomes associated with emerging agents that are hepatokine-modulating, islet-targeted, or beta-cell protective, or involved in combination therapies and fixed-dose regimens will not be addressed[14]. Such agents exhibit no safety red flag related to cardiometabolic disease and are not monitored in phase III clinical trials for those effects [13].

Clinical Trial Landscape and Regulatory Perspectives

Novel pharmacotherapies for type 2 diabetes: present evidence-based, objective analysis and synthesize mechanisms, efficacy, safety, and translational relevance across populations [12].

Phase I–III Trial Design for Novel Agents

Owing to an urgent need for more effective type 2 diabetes management, a growing number of novel therapeutic agents are undergoing clinical testing [13]. For regulatory approval, most of these compounds aim to demonstrate significant improvements in glycemic control and weight change, typically with respective endpoints of HbA1c and bodyweight or BMI. For agents targeting established pharmacological pathways considered indirectly or secondarily effective, additional diabetes-related endpoints are often required [11]. Thus, phase I–III designs adequately validate efficacy and safety of investigational compounds targeting new pathways such as incretin, SGLT2, or branched-chain amino acid metabolism, which collectively cause type 2 diabetes and associated comorbidities across age and ethnicity [22]. Postcontextual factors can further shape yet recurrently hamper the agent's development of the advanced compounds [23].

Regulatory Pathways and Postmarket Surveillance

As highlighted in recent reviews, the regulatory pathways for approval of novel pharmacotherapies for T2D are complex and may differ from those for T1D [23]. The presence of multiple cardiovascular outcome studies (CVOS) for candidate therapies indicated that insulin and glucagon would have to be evaluated for their atherogenic risk before formal consideration of either compound by regulatory authorities [24]. Despite the substantial population affected by T2D, several candidates theoretically having a disease-modifying mechanism have entered clinical trials without broad regulatory experience for diabetes therapies [23]. Consequently, the development of pathogenic assays for potentially disease-modifying agents would coexist with the drug evaluation process. T2D interventions generally carry fewer conditions than those for other conditions, although achievement of insulin independence may still lead to duration-related requirements. The risk of secondary failure during the preclinical phase remains an important consideration for the entire T2D field [25]. Development and acceptance of T2D agents may differ among geographic regions. Significant paracrine activity within the pancreas may restrict candidate selection for agents intended to target T2D via β-cell re-functioning or protection in certain regions. Ochratoxin [23], which causes type 1-like diabetes, and other environmental triggers initiate or accelerate T1D cycles by acting at multiple game-theoretic equilibria. Certain stimuli characteristic of T1D animals increase the incidence of T2D and decrease fertility, resulting in selection against T1D over evolutionary time when the frequency of T2D remains stable [18]. Nutri-cider and complementary agents providing a specific and assay-acceptable perturbation of T1D flavors for T2D field edge-effect testing substantially reduce the entry of ability-to-cure T1D β-cell simulants and the range of T1D combination therapies that also offer T2D benefits. Standard exploratory studies are therefore not necessarily sufficient to classify certain candidates as merely attenuating T1D or T2D [22].

Equity and Accessibility Considerations

Equity and accessibility considerations are paramount in diabetes treatment [24]. Given a choice, current recommendations suggest that metformin remains the first-line agent of choice for the management of T2D; newer agents should be selected accordingly in the second-line, third-line, and fourth-line therapies [21]. In developing countries, treating T2D continues to be a major challenge [23]. Out of the total of 405 million people with diabetes worldwide, nearly half of these are living in rural areas of developing countries, where they neither receive proper treatment nor awareness [20]. Countries with lower per capita expenditure on health are likely to spend up to 35% of their health budget on diabetes, where expenditure on diabetes treatment further increases when economic growth occurs [19].

Implementation in Clinical Practice

The management of type 2 diabetes can benefit from improved patient selection [5]. The sequencing and combination of pharmacotherapies should be adapted to patient characteristics to maximize benefits and mitigate risks [5]. The approaches discussed in previous sections can, in principle, be guided by pharmacokinetic and pharmacodynamic considerations, patient-specific biomarkers, individual safety profiles, and added cardiometabolic benefits. Such consideration may prove to be particularly useful in vulnerable populations, including patients with

prevalent CVD or renal impairment, the elderly, and individuals with multiple comorbidities or polypharmacy [3]. Despite the potential of existing therapies to enhance glycemic control and mitigate adverse effects, insufficient attention often focuses on achieving the desired glycemic goal [25]. Weight gain and hypoglycemia are the most common consequences of glucose-lowering agents [24]. Patient motivation and confidence, perceived benefit versus cost of treatment, and medication adherence also play crucial roles in therapy 25. Individualized approaches that combine various antidiabetic agents targeting distinct pathophysiological defects or that select an agent suitable for the specific patient are therefore warranted [23].

Patient Selection and Individualized Therapy

Appropriate selection of therapies for type 2 diabetes requires a clear understanding of clinical characteristics and pathophysiological mechanisms [25]. To guide the selection of pharmacologic agents and interventions in individuals with type 2 diabetes and cardiometabolic disease, the Italian Diabetes Society has introduced an algorithm based on major clinical phenotypes [24]. The initial step is to determine or characterize the clinical phenotype related to abnormal glucose metabolism and the additional presence of significant cardiovascular or renal disease, identifying just one signature for selection of the most appropriate therapy [20]. Personalized medication choice and combination treatment will improve safety and adherence to the regimen by ensuring that the drug targets the determined metabolic defect [20]. The rise in the incidence of type 2 diabetes has accelerated greatly due to both genetic and environmental factors, with patients progressing at different rates to hyperglycemia associated with heterogeneous pathophysiological defects [23]. After many years of research, elucidation of the various clinical and biological sub-phenotypes of the disease is essential for further rationalization of treatment approaches and to prevent cardiovascular mortality and complications [24]. Continually accumulating evidence suggests that an algorithmic approach based on the identification of clinical phenotypes and their principal determinants will facilitate selection of safer and more effective treatment strategies [26, 27].

Monitoring and Dose Optimization

The accurate assessment of the pharmacological treatment for diabetes requires frequent monitoring of blood glucose levels, thus determining the needed dosage of drugs [24]. These dosages should be based on the active blood glucose level and should be adjusted according to the drug the patient is under, metabolic status, and other relevant markers [3]. In general, based on the blood glucose concentration considered and/or the time from the last dose taken, drugs can be classified as short, intermediate, or long-acting [28]. The following table summarizes the trade-off considerations between the anticipated therapeutic effect and its associated adverse effects[7]. The selection of a glucose-lowering treatment strategy in a patient is based on a combination of considerations, including the HbA1c target to be achieved, the presence of cardiovascular disease, chronic kidney disease, age, and weight [27]. Given the diversity of oral classes and injectable agents available, the selection also takes into account the anticipated level of clinical inertia to avoid underdosing [26]. Therefore, if it may take considerable time to step up the dosage, selecting a drug with a high efficacy for the predetermined target is crucial. Moreover, specific agents offer advantages in patients with heart failure or chronic kidney disease. When combining different medications, it is necessary to consider the risk and type of adverse effects from each compound [25].

Practical Considerations in Special Populations

As of 2015, an estimated 415 million individuals globally had diabetes, with a prevalence of 10% in adults aged 20–79 years [24]. The International Diabetes Federation (IDF) projects an increase to 642 million by 2040 if left untreated. The 414 million with type 2 diabetes constitute 85%–95% of all individuals with diabetes, with 75%–85% of all cases remaining undiagnosed [29]. The worldwide number of people with type 2 diabetes is expected to rise to 578 million by 2030 and 700 million by 2045. By 2030, India will account for one-sixth of the worldwide burden of diabetes [29-37].

CONCLUSION

The management of type 2 diabetes is increasingly informed by the development of novel pharmacotherapies targeting multiple pathophysiological mechanisms. Agents such as GLP-1 receptor agonists, dual incretin receptor agonists, SGLT2 inhibitors, and hepatokine modulators provide enhanced glycemic control, cardiometabolic benefits, and weight management, while islet-targeted strategies aim to preserve or restore β-cell function. Personalized treatment approaches, guided by patient-specific phenotypes, biomarkers, and pharmacokinetic/pharmacodynamic considerations, are essential to optimize outcomes and minimize adverse effects. Combination therapies and fixed-dose regimens further improve efficacy and adherence. Despite challenges in accessibility and equitable distribution, especially in developing countries, these innovations represent a significant step toward improving T2DM management, reducing complications, and enhancing patient quality of life globally.

REFERENCES

1. Dahlén AD, Dashi G, Maslov I, Attwood MM, Jonsson J, Trukhan V, Schiöth HB. Trends in antidiabetic drug discovery: FDA-approved drugs, new drugs in clinical trials, and global sales. Frontiers in Pharmacology. 2022 Jan 19;12:807548.
2. Tahrani AA, Barnett AH. Dapagliflozin: a sodium glucose cotransporter 2 inhibitor in development for type 2 diabetes. Diabetes Therapy. 2010 Dec;1(2):45-56.
3. Ugwu OP, Ogenyi FC, Ugwu CN, Basajja M, Okon MB. Mitochondrial stress bridge: Could muscle-derived extracellular vesicles be the missing link between sarcopenia, insulin resistance, and chemotherapy-induced cardiotoxicity?. Biomedicine & Pharmacotherapy. 2025 Dec 1;193:118814.
4. Scheen AJ. Pharmacological management of type 2 diabetes: what's new in 2017?. Expert review of clinical pharmacology. 2017 Dec 2;10(12):1383-94.
5. Sena CM, Bento CF, Pereira P, Seiça R. Diabetes mellitus: new challenges and innovative therapies. EPMA Journal. 2010 Mar;1(1):138-63.
6. Cornell S. Continual evolution of type 2 diabetes: an update on pathophysiology and emerging treatment options. Therapeutics and clinical risk management. 2015 Apr 16:621-32.
7. Paul-Chima UO, Nneoma UC, Bulhan S. Metabolic immunobridge: Could adipose-derived extracellular vesicles be the missing link between obesity, autoimmunity, and drug-induced hepatotoxicity?. Medical Hypotheses. 2025 Sep 28:111776.
8. Cernea S, Raz I. Therapy in the early stage: incretins. Diabetes care. 2011 May 1;34(Supplement_2):S264-71.
9. Nisal K, Kela R, Khunti K, Davies MJ. Comparison of efficacy between incretin-based therapies for type 2 diabetes mellitus. BMC Medicine. 2012 Nov 30;10(1):152.
10. Bastin M, Andreelli F. Dual GIP–GLP1-receptor agonists in the treatment of type 2 diabetes: a short review on emerging data and therapeutic potential. Diabetes, metabolic syndrome and obesity: targets and therapy. 2019 Sep 30:1973-85.
11. Jiménez-Martí E, Hurtado-Genovés G, Aguilar-Ballester M, Martínez-Hervás S, González-Navarro H. Novel therapies for cardiometabolic disease: recent findings in studies with hormone peptide-derived g protein coupled receptor agonists. Nutrients. 2022 Sep 13;14(18):3775.
12. Ugwu OP, Ogenyi FC, Ugwu CN, Ugwu MN. Gut microbiota-derived metabolites as early biomarkers for childhood obesity: A policy commentary from urban African populations. Obesity Medicine. 2025 Sep 1;57:100641.
13. Maccari R, Ottanà R. Sodium-glucose cotransporter inhibitors as antidiabetic drugs: current development and future perspectives. Journal of medicinal chemistry. 2022 Aug 4;65(16):10848-81.
14. Gastaldelli A, Stefan N, Häring HU. Liver-targeting drugs and their effect on blood glucose and hepatic lipids. Diabetologia. 2021 Jul;64(7):1461-79.
15. Patel P. Treatment Landscape of Metabolic-Dysfunction-Associated Steatotic Liver Disease. Journal of Clinical Medicine. 2025 Aug 27;14(17):6060.
16. Portha B, Tourrel-Cuzin C, Movassat J. Activation of the GLP-1 receptor signalling pathway: a relevant strategy to repair a deficient beta-cell mass. Journal of Diabetes Research. 2011;2011(1):376509.
17. Castro-Gutierrez R, Michels AW, Russ HA. β Cell replacement: improving on the design. Current Opinion in Endocrinology, Diabetes and Obesity. 2018 Aug 1;25(4):251-7.
18. Barnard K, Cox ME, Green JB. Clinical utility of fixed combinations of sitagliptin–metformin in treatment of type 2 diabetes. Diabetes, metabolic syndrome and obesity: targets and therapy. 2010 Oct 27:363-72.
19. Ugwu OP, Okon MB, Alum EU, Ugwu CN, Anyanwu EG, Mariam B, Ogenyi FC, Eze VH, Anyanwu CN, Ezeonwumelu JO, Egba SI. Unveiling the therapeutic potential of the gut microbiota–brain axis: Novel insights and clinical applications in neurological disorders. Medicine. 2025 Jul 25;104(30):e43542.
20. Levin PA. Practical combination therapy based on pathophysiology of type 2 diabetes. Diabetes, metabolic syndrome and obesity: Targets and therapy. 2016 Oct 31:355-69.
21. DiStefano JK, Watanabe RM. Pharmacogenetics of anti-diabetes drugs. Pharmaceuticals. 2010 Aug 13;3(8):2610-46.
22. Rathmann W, Bongaerts B. Pharmacogenetics of novel glucose-lowering drugs. Diabetologia. 2021 Jun;64(6):1201-12.
23. Park JE, Jeong GH, Lee IK, Yoon YR, Liu KH, Gu N, Shin KH. A pharmacometabolomic approach to predict response to metformin in early-phase type 2 diabetes mellitus patients. Molecules. 2018 Jun 29;23(7):1579.

24. Ugwu CN, Ugwu OP, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI, Uti DE. Sustainable development goals (SDGs) and resilient healthcare systems: Addressing medicine and public health challenges in conflict zones. Medicine. 2025 Feb 14;104(7):e41535.
25. Son JW, Kim S. Dipeptidyl peptidase 4 inhibitors and the risk of cardiovascular disease in patients with type 2 diabetes: a tale of three studies. Diabetes & metabolism journal. 2015 Oct 22;39(5):373.
26. von Lewinski D, Kolesnik E, Wallner M, Resl M, Sourij H. New antihyperglycemic drugs and heart failure: synopsis of basic and clinical data. BioMed Research International. 2017;2017(1):1253425.
27. Kim NH, Lim S, Kwak SH, Moon MK, Moon JS, Lee YH, Cho HC, Lee J, Kim SG. Efficacy and tolerability of novel triple combination therapy in drug-naïve patients with type 2 diabetes from the TRIPLE-AXEL trial: protocol for an open-label randomised controlled trial. BMJ open. 2018 Sep 1;8(9):e022448.
28. Mittermayer F, Caveney E, De Oliveira C, Alexander Fleming G, Gourgiotis L, Puri M, Tai LJ, Rick Turner J. Addressing unmet medical needs in type 1 diabetes: a review of drugs under development. Current Diabetes Reviews. 2017 Jun 1;13(3):300-14.
29. Mohan V, Khunti K, Chan SP, Filho FF, Tran NQ, Ramaiya K, Joshi S, Mithal A, Mbaye MN, Nicodemus Jr NA, Latt TS. Management of type 2 diabetes in developing countries: balancing optimal glycaemic control and outcomes with affordability and accessibility to treatment. Diabetes Therapy. 2020 Jan;11(1):15-35.
30. Edyedu I, Ugwu OP, Ugwu CN, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI. The role of pharmacological interventions in managing urological complications during pregnancy and childbirth: A review. Medicine. 2025 Feb 14;104(7):e41381.
31. Kuritzky L, Samraj GP. Enhanced glycemic control with combination therapy for type 2 diabetes in primary care. Diabetes Therapy. 2011 Sep;2(3):162-77.
32. Ceriello A, Gallo M, Candido R, De Micheli A, Esposito K, Gentile S, Medea G. Personalized therapy algorithms for type 2 diabetes: a phenotype-based approach. Pharmacogenomics and personalized medicine. 2014 Jun 19:129-36.
33. Paul-Chima UO, Ugwu CN, Alum EU. Integrated approaches in nutraceutical delivery systems: optimizing ADME dynamics for enhanced therapeutic potency and clinical impact. RPS Pharmacy and Pharmacology Reports. 2024 Oct;3(4):rqae024.
34. Esposito K, Gentile S, Candido R, De Micheli A, Gallo M, Medea G, Ceriello A. Management of hyperglycemia in type 2 diabetes: evidence and uncertainty. Cardiovascular diabetology. 2013 May 30;12(1):81.
35. Li HY. Revisiting the strategies for the pharmacological management of type 2 diabetes–From glycemic control, organ protection, safety to weight reduction. Journal of diabetes investigation. 2022 Jan;13(1):3-5.
36. Alum E, PC U, Obeagu E, Aja P, Ugwu C, Okon M. Nutritional Care in Diabetes Mellitus: A Comprehensive Guide. 11, 16–15 (2023) [Internet].
37. Capuano A, Sportiello L, Maiorino MI, Rossi F, Giugliano D, Esposito K. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapy–focus on alogliptin. Drug design, development and therapy. 2013 Sep 17:989-1001.

CITE AS: Kintuza Lumwako Tebulo. (2026). Novel Pharmacotherapies for Type 2 Diabetes. IDOSR JOURNAL OF SCIENTIFIC RESEARCH 11(1):131-138. https://doi.org/10.59298/IDOSRJSR/2026/11.1.131138