WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 18, 81-85. Review Article ISSN 2277–7105

A REVIEW ON CLINICAL PHARMACOLOGY OF NOVEL ANTIDIABETIC AGENTS: MECHANISMS, EFFICACY, AND SAFETY INSIGHTS

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Article Received on
23 July 2025,

Revised on 12 August 2025,
Accepted on 01 Sept. 2025

DOI: 10.20959/wjpr202518-38225

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ABSTRACT

Diabetes mellitus remains one of the most pressing global health challenges. The limitations of conventional therapies, including sulfonylureas, metformin, and insulin, have necessitated the development of novel antidiabetic agents. This review summarizes the clinical pharmacology of recently introduced drug classes such as DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and emerging dual multi-agonists. We discuss their mechanisms of action, pharmacokinetic and pharmacodynamic profiles, efficacy outcomes, safety considerations, and roles in special populations. Additionally, we highlight future perspectives including pharmacogenomics, personalized medicine, digital therapeutics, and sustainable green pharmacology. These advancements underscore the paradigm shift from glucose-centric therapy to holistic cardiometabolic care in type 2 diabetes management.

KEYWORDS: Clinical pharmacology, Novel antidiabetic agents, SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, Pharmacokinetics, Diabetes management, Safety profile.

1. INTRODUCTION

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), has emerged as a global epidemic, with significant implications for morbidity, mortality, and healthcare expenditure. Conventional therapeutic strategies such as sulfonylureas, metformin, and insulin, while effective for glycemic control, are limited by adverse effects including hypoglycemia, weight gain, and restricted cardiovascular benefit. This has led to the development of novel classes of antidiabetic drugs that target diverse pathways in glucose homeostasis while offering additional benefits such as weight reduction, cardiovascular protection, and renal safety. This review provides an overview of the clinical pharmacology of novel antidiabetic agents with a focus on mechanisms of action, efficacy, safety, and future perspectives.

2. Novel Antidiabetic Agents – Clinical Pharmacology Perspective

2.1 DPP-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors enhance endogenous incretin activity by preventing the breakdown of GLP-1 and GIP. Drugs such as sitagliptin, vildagliptin, and linagliptin improve glycemic control with modest efficacy and minimal risk of hypoglycemia. Pharmacokinetically, most are orally bioavailable with once-daily dosing, though renal dose adjustments may be required except for linagliptin. They are weight-neutral and generally well-tolerated, making them suitable for elderly or comorbid patients.

2.2 GLP-1 Receptor Agonists

GLP-1 receptor agonists (GLP-1 RAs) such as liraglutide, exenatide, semaglutide, and dulaglutide mimic endogenous GLP-1, enhancing insulin secretion, suppressing glucagon release, and slowing gastric emptying. They are associated with clinically significant reductions in HbA1c, weight loss, and cardiovascular risk. Pharmacologically, these agents vary in half-life, allowing for daily or weekly administration. Adverse effects primarily include gastrointestinal intolerance, while rare risks include pancreatitis and medullary thyroid carcinoma.

2.3 SGLT2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, including empagliflozin, dapagliflozin, and canagliflozin, reduce renal glucose reabsorption, leading to glucosuria and modest reductions in body weight and blood pressure. Beyond glycemic control, SGLT2 inhibitors have demonstrated significant cardiovascular and renal protection, including reduced risk of heart failure hospitalization and slowing of chronic kidney disease progression. Adverse

effects include genitourinary infections, volume depletion, and rare cases of diabetic ketoacidosis.

2.4 Dual and Multi-Agonists

Tirzepatide, a dual GIP and GLP-1 receptor agonist, has shown superior glycemic and weight reduction compared to GLP-1 RAs alone. Emerging research on triple agonists targeting GLP-1, GIP, and glucagon receptors promises enhanced efficacy, though long-term safety and tolerability require further study.

3. Comparative Efficacy – Clinical Trial Insights

Landmark cardiovascular outcome trials (CVOTs) have highlighted the superiority of novel antidiabetic drugs in reducing major adverse cardiovascular events (MACE) and renal complications. For instance, EMPA-REG OUTCOME demonstrated significant cardiovascular mortality reduction with empagliflozin, while LEADER and SUSTAIN-6 confirmed the cardiovascular safety and benefit of liraglutide and semaglutide, respectively. Tirzepatide trials (SURPASS) suggest potential paradigm shifts in treatment algorithms by outperforming existing GLP-1 RAs.

4. Safety and Adverse Drug Reactions

The safety profile of novel antidiabetic agents is generally favorable. DPP-4 inhibitors have minimal adverse effects, while GLP-1 RAs are commonly associated with nausea, vomiting, and diarrhea. SGLT2 inhibitors carry risks of genitourinary infections, volume depletion, and rare euglycemic diabetic ketoacidosis. Safety considerations for dual agonists are evolving, with gastrointestinal side effects being the most common. Long-term safety surveillance remains essential.

5. Clinical Use in Special Populations

Clinical use in special populations requires tailored strategies. In elderly patients, DPP-4 inhibitors are preferred for their safety, while GLP-1 RAs and SGLT2 inhibitors provide additional benefits in obese or cardiorenal patients. Pregnant and pediatric populations lack sufficient trial data, limiting widespread use. Patients with chronic kidney disease benefit from SGLT2 inhibitors, though dose adjustments and careful monitoring are critical.

6. Future Directions in Clinical Pharmacology

Future directions include the integration of pharmacogenomics to enable personalized therapy, development of dual and multi-agonist drugs with superior efficacy, and expanded trials in special populations. Additionally, AI-driven monitoring, digital therapeutics, and green pharmacology practices will play a critical role in ensuring sustainability in drug development and clinical practice.

7. CONCLUSION

Novel antidiabetic agents represent a paradigm shift in diabetes management, offering benefits that extend beyond glucose control to cardiovascular and renal protection. DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors have become integral to modern therapy, while dual/multi-agonists promise a new era of personalized treatment. Clinical pharmacology must evolve to incorporate pharmacogenomics, AI tools, and sustainable practices to ensure therapies are effective, safe, and environmentally responsible.

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