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Review Article

SAFETY AND EFFICACY OF PROTRACTED USAGE OF ORAL ANTIDIABETIC DRUGS IN TYPE-2 DIABETES MANAGEMENT

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ABSTRACT

This review paper explores the impact of prolonged usage of oral antidiabetic drugs (OADs), particularly focusing on the therapeutic benefits and adverse effects associated with long-term consumption of these medications. Diabetes mellitus is becoming increasingly common worldwide, with 415 million adults diagnosed in 2015 and an anticipated increase to 642 million by 2040. Successfully treating type 2 diabetes typically involves a multi-faceted approach, targeting both insulin resistance and impairing the function of endocrine beta-cell using multiple medications. Although metformin is commonly regarded as the primary oral medication for diabetes management, it may not always provide adequate control, prompting the need for supplementary therapies to enhance its efficacy. Among the various oral antidiabetic agents available, sulfonylureas, such as glimepiride, remain a popular choice as a second-line add-on to metformin, particularly in Indian clinical settings. Compared to conventional sulfonylureas such as glibenclamide, modern sulfonylureas such as glimepiride have shown improved outcomes and better safety profiles. Glimepiride has been extensively studied and has a large body of evidence supporting its use. Nevertheless, antidiabetic medications have shown limited success in attaining ideal blood sugar control, with merely 41% of individuals reaching the intended goals. In adition, questions have been raised regarding the possible harmful effects and adverse reactions of these drugs, such as increased body weight, decreased bone density, and heightened risk of heart-related issues. The use of sulfonylureas has been linked to heightened risks of low blood sugar, increased body mass, and harm to the cardiovascular system. In contrast, the usage of metformin may lead to digestive system discomfort. Despite potential risks, the advantages of these drugs, including better blood sugar management, kidney protection, and fewer diabetes-related complications, generally surpass the possible drawbacks when used carefully. In response to these issues, scientists have investigated alternative strategies to reduce long-term use of antidiabetic medications.

Keywords: Diabetes, Oral anti diabetic drugs, Insulin, Metformin, Glimepiride, DPP4 inhibitors.

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INTRODUCTION

Diabetes is a complex condition marked by elevated glucose levels in the blood, stemming from either a deficiency in insulin secretion, impaired insulin function, or a combination of both factors. This condition affects the metabolism of carbohydrates, fats, and proteins. Prolonged exposure to this condition leads to micro and macro complications which affect the vital system, such as the circulatory, excretory, and visual system. Global diabetes incidence and its prevalence have increased, especially in developing nations, which made it a significant public health issue. Projections indicate that these numbers will continue to rise in the coming years [1-3].

CLASSIFICATION OF DIABETES

Type 1 and Type 2 are the two primary categories of diabetes mellitus. These classifications are based on several factors, including the age at when the disease first appears, the extent of beta cell role deterioration, the degree of insulin resistance, the existence of diabetes-related autoantibodies, and whether insulin treatment is essential for survival. Across the spectrum of diabetes, one consistent feature emerges: an excess of sugar in the bloodstream, they differ in their root causes, disease mechanisms, progression patterns, and treatment strategies [1-4].

TYPE-1 DIABETES MELLITUS (T1DM)

Insulin-dependent diabetes mellitus, or T1DM or juvenile-onset diabetes, is defined by the destruction of beta cells in the pancreas, usually caused by autoantibodies or unknown factors, resulting in a lack of insulin [5,6]. Patients with this condition must receive external insulin throughout their lives to survive and maintain glucose balance. While T1DM is frequently diagnosed in young individuals, it can also affect adults, comprising 5–10% of all diabetes cases. The speed at which autoimmune destruction of pancreatic beta cells occurs varies among individuals. This process can be identified by testing for autoantibodies, including those targeting glutamic acid decarboxylase and tyrosine phosphatases IA-2 and IA-2β. The American Diabetes Association classifies cases where 85–90% of patients exhibit one or more of these autoantibodies as immune-mediated diabetes mellitus. Another variant, termed idiopathic diabetes, has an unidentified cause. The American Diabetes Association notes that this form applies to select diabetes cases and is characterized by periodic ketoacidosis. Its worth noting that type 1 diabetes can manifest in both childhood and adulthood. The diabetic symptoms, which include weight reduction, polyuria, polydipsia, and polyphagia and these manifestations were common to both types of diabetes. However, diabetic ketoacidosis is specific to type 1 diabetes, the insulin-dependent form. In general, the arrival of symptoms in T1DM is more rapid compared to Type 2.

TYPE-2 DIABETES MELLITUS (T2DM)

Non-insulin-dependent diabetes, also known as adult-onset diabetes or T2DM, is a condition marked by high blood sugar levels and disruptions in the body's processing of carbohydrates, fats, and proteins. This disorder results from either the body's resistance to insulin or a relative lack of insulin production. Type 2 diabetes is the predominant form of the disease, comprising approximately 90–95% of all diagnosed cases. When diabetes is suspected, four crucial biochemical tests are used for diagnosis: blood sugar measurements taken while fasting and after consuming 75 g of glucose (postprandial), HbA1c levels, and random

blood glucose readings. In the early stages of type 2 diabetes, patients do not exhibit typical symptoms associated with diabetes, such as weight reduction, increased thirst, and frequent urination. This absence of symptoms is attributed to the slow evolution of insulin resistance and gradually decline in beta cell function [7].

DRUG-INDUCED DIABETES

Various medications can elevate blood glucose levels in people who already have insulin resistance, despite not directly causing diabetes. These include pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, beta-adrenergic agonists, and thiazide diuretics. It is crucial to closely monitor patients taking these medications for signs of hyperglycemia [8].

GESTATIONAL DIABETES

Typically happening in the second or third trimester of pregnancy, gestational diabetes can affect expectant mothers. Although some women's blood sugar levels may return to normal after delivery, others could have a higher likelihood of developing T2DM in the future.

OTHER TYPES OF DIABETES (AMERICAN DIABETES ASSOCIATION 2014)

Beyond the main categories of diabetes, researchers have identified various less prevalent forms. These include genetic mutations affecting the function of pancreatic beta cells or insulin effectiveness, diseases of the exocrine pancreas, disorders of the endocrine system, certain infections, uncommon autoimmune-related diabetes, and inherited syndromes linked to disrupted glucose metabolism.

PREDISPOSING FACTORS FOR TYPE 2 DIABETES

Various elements contribute to developing type 2 diabetes. These can be generally classified as:

Unalterable risk factors

- Heredity: The presence of type 2 diabetes in a parent, sibling, or close family member significantly elevates one's risk
- Advancing Years: The probability rises with age, especially after 45 [10]. Although it can manifest in younger individuals, it is more common among older adults
- Racial Background: Certain racial groups and Pacific Islander communities face a higher likelihood
- Inherited Susceptibility: While not completely elucidated, genetic factors play a part. Some individuals are genetically more prone to developing insulin resistance
- Prior Gestational Diabetes: Pregnant women who develop gestational diabetes are at a significantly increased risk of progressing to type 2 diabetes in the future
- Polycystic ovary syndrome (PCOS): Women diagnosed with PCOS are one of the causes for elevated type 2 diabetes.

Alterable risk factors

- Excess Weight and Obesity: Carrying extra pounds, particularly in the midsection, is a significant risk element [9,10]. Adipose tissue can hinder the body's ability to utilize insulin effectively
- Sedentary Lifestyle: Insufficient regular exercise elevates risk [10]. Physical activity enhances insulin sensitivity
- Poor Dietary Habits: Consuming foods high in saturated and trans fats, highly processed items, and sugar-laden beverages increases risk [11]
- Elevated Blood Pressure: Hypertension frequently accompanies type 2 diabetes [10]
- Imbalanced Cholesterol: Elevated low-density lipoprotein cholesterol and reduced high-density lipoprotein cholesterol levels heighten risk [10]
- Prediabetes: This condition, characterized by impaired fasting glucose or impaired glucose tolerance, indicates blood sugar levels above normal but below diabetic thresholds. Prediabetes substantially increases the likelihood of developing type 2 diabetes [10]
- Mental Stress: Research indicates a connection between long-term stress and an elevated risk of T2DM.

It's crucial to understand that possessing one or more risk factors doesn't necessarily lead to type 2 diabetes. However, recognizing your risk factors can guide you in making lifestyle choices to minimize your risk.

MANIFESTATIONS OF TYPE 2 DIABETES

The onset of T2DM is initially experienced as no discernible symptoms. This underscores the importance of routine check-ups and screenings, particularly for those with risk factors.

When symptoms do manifest, they may include:

- Excessive Thirst: Experiencing unusual levels of thirst
- Polyuria: Increased urination, particularly during nighttime
- Polyphagia: Feeling hungry despite having eaten
- Unintended Weight Reduction: Despite an increase in appetite
- Visual Disturbances: Elevated blood sugar levels affecting eyesight
- Delayed Wound Healing: High blood glucose can compromise the body's healing processes
- Recurrent Infections: Including candidiasis or urinary system infections
- Paresthesia: Sensations of numbness or tingling in extremities (peripheral neuropathy)
- Exhaustion: Experiencing weakness and tiredness
- Xerosis: Dry, itchy skin resulting from dehydration.

It's crucial to understand that not all individuals with type 2 diabetes will exhibit every symptom. Some may experience only a few mild manifestations, while others might face more severe symptoms. If you notice any of these signs, it's vital to seek medical advice for proper diagnosis and management. Timely identification and treatment can help mitigate or postpone the development of serious complications.

These symptoms can range in intensity and may not always be immediately noticeable, potentially leading to a delayed diagnosis.

COMPLICATIONS AND MANAGEMENT

Diabetes can have detrimental effects on various critical organ systems. Over time, it may give rise to serious complications that can be classified as either microvascular or macrovascular. Microvascular issues encompass damage to nervous tissue, renal tissue, and ocular structures. Macrovascular pathologies, on the other hand, lead to disorders of the heart, blood vessels, and peripheral vasculature. The peripheral vascular disease associated with diabetes can precipitate non-healing ulcers, gangrene, and ultimately, limb amputation [12]. The microvascular complications of diabetes are responsible for a significant proportion of the morbidity and mortality experienced by those living with the disease.

MICROVASCULAR

Retinopathy

Among individuals with diabetes, diabetic retinopathy stands as the most common microvascular complication, causing more than 10,000 new instances of blindness each year. This condition, linked to chronic hyperglycemia, can develop gradually and may manifest up to 7 years before the clinical diagnosis of T2DM. Between 1997 and 2005, women with diabetes were more susceptible to visual impairment than men. However, since 2001, the prevalence rate among women has shown a consistent decrease, while remaining stable for men [13]. During this period, prevalence was similar across different racial groups. For those with type 2 diabetes, the length of time they have had the disease is a crucial predictor of vision loss. Importantly, about 90% of blindness caused by retinopathy in diabetic patients can be averted through early detection and proper treatment. As a result, annual dilated eye exams are recommended for all diabetic patients [14].

Neuropathy

Diabetic peripheral neuropathy, a frequent complication of long-term diabetes, is believed to affect between 30% and 50% of patients. Unregulated blood glucose levels are the main contributing factor, with additional risk factors including patient age, early disease onset, unmanaged hypertension, tobacco use, high triglyceride levels, increased body mass index, alcohol intake, and greater height. Most cases of diabetic peripheral neuropathy involve a chronic, distal symmetric polyneuropathy. This condition can cause sensory loss, muscular weakness, and heightened pain sensitivity. The polyneuropathy typically progresses gradually, with patients often experiencing unnoticed sensory impairment, burning sensations, and loss of feeling in their feet for extended periods. Approximately 11–32% of individuals with this condition suffer from neuropathic pain, which can be intense. The National Centre for Health Statistics data indicate that the proportion of hospital discharges attributed to diabetic peripheral neuropathy showed gradual improvement between 1996 and 2003. For patients with this condition, the age-adjusted hospital discharge rate rose from 4.7 per 1,000 in 1996 to 6.8 in 2003. Discharge rate estimates were higher among younger males compared to both females and older men [15-19].

Nephropathy

Persistent proteinuria without urinary tract infection or other causes is a hallmark of diabetic nephropathy. While clinical nephropathy typically develops later in type 1 diabetes, whereas in T2DM, proteinuria may be present at the time of diagnosis. The occurrence of diabetic nephropathy in type 2 diabetes patients remains low for the initial 10–15 years after disease onset, then swiftly rises to a peak around 18 years of duration, before decreasing. The high prevalence of nephropathy at diabetes diagnosis is attributed to the actual onset of type 2 diabetes often preceding clinical diagnosis by several years, resulting in complications due to delayed detection. In 2002, diabetes-related nephropathy was responsible for 44% of new end-stage renal disease cases, with approximately 153,730 patients with ESRD due to diabetes receiving kidney transplants or undergoing chronic dialysis [20]. The precise cause of diabetic nephropathy remains unclear, but various risk factors, both modifiable and non-modifiable, contribute to its development. Metabolic control is a significant modifiable risk factor, as strict glycaemic management in both type 1 and type 2 diabetes substantially lowers the risk of microalbuminuria and persistent proteinuria. Hypertension also elevates the risk of renal failure in diabetes, although it is uncertain whether high blood pressure at diabetes onset directly causes nephropathy. Additional proposed risk factors include elevated body mass index, smoking, anaemia, obesity, and genetic components [21-23]. Type 2 diabetes patients with diabetic nephropathy are more vulnerable to various diabetes-related complications, including the renal-retinal syndrome. These individuals also face a higher likelihood of developing ischemic heart disease and stroke compared to diabetics without nephropathy and are more prone to succumbing to macrovascular diseases [24]. In recent decades, the incidence of diabetic nephropathy has decreased, likely due to advancements in disease management, such as stricter control of blood sugar levels and improved hypertension management. This trend is supported by a comparison of four cohorts of individuals with type 1 diabetes identified between 1965 and 1984, which demonstrated the lowest cumulative incidence of diabetic nephropathy over time [25,26].

MACROVASCULAR

Cardiovascular disease and stroke

Diabetes-related cardiovascular disease is the primary cause of death, responsible for approximately 65% of all fatalities. The most prevalent health issues linked to diabetes are coronary artery disease and stroke. Individuals with diabetes face 2–4 times higher mortality rates from cardiovascular disease and an increased likelihood of stroke compared to those without diabetes. Furthermore, over 70% of diabetic patients experience high blood pressure or use antihypertensive drugs. More research is needed to understand how elevated blood sugar levels contribute to cardiovascular complications in diabetic patients [27-29]. The factors that increase cardiovascular disease risk in diabetic and non-diabetic populations are similar, including tobacco use, high blood pressure, and abnormal lipid levels. However, these risk factors have a more pronounced impact on individuals with diabetes. Studies have tracked diabetic cardiovascular disease outcomes from the 1950s to 2003 across various demographics and regions. A significant decrease in cardiovascular disease incidence has been observed over time, with the most substantial reduction occurring between the 1980s and 1990s, coinciding with improvements in managing high blood sugar, hypertension, and abnormal lipid levels. However, this progress has stagnated since the late 1990s. Diabetic patients have a 1.5–3 times higher risk of experiencing a stroke compared to non-diabetic individuals [29-31].

Peripheral vascular disease

Peripheral arterial disease, also referred to as peripheral vascular disease, is characterized by the constriction of blood vessels that provide blood to the extremities, abdomen, and kidneys. Individuals with diabetes face a heightened risk of developing this condition, with the likelihood increasing based on factors such as age at diabetes onset, duration of the disease, and the presence of neuropathy. According to data from the National Center for Health Statistics, there has been a steady decrease in hospital discharges for peripheral arterial disease as the primary diagnosis since 1996 [32,33]. The risk of peripheral arterial disease is exacerbated by elevated levels of certain substances associated with cardiovascular disease, such as C-reactive protein and homocysteine. Two primary symptoms experienced by patients with this condition are intermittent claudication and rest pain. Peripheral arterial disease significantly increases the risk of lower limb amputation [35].

MANAGEMENT

Effective diabetes management requires a multifaceted approach, combining lifestyle adjustments such as dietary changes and physical activity with individualized medication regimens. As type 2 diabetes advances, it becomes necessary to supplement lifestyle modifications with oral medications to maintain proper blood glucose control. Some patients may require multiple drugs, including insulin therapy, to reach their target blood sugar levels. The overarching aim of diabetes treatment is to avert complications associated with the condition.

INSULIN

While insulin is primarily utilized for treating type 1 diabetes, it can also prove advantageous for those with type 2 diabetes whose pancreatic insulin production is minimal or non-existent, or when oral medications fail to sufficiently regulate blood glucose levels. The effectiveness of insulin therapy in managing diabetes stems from its ability to directly substitute the insulin that the body cannot produce, thus helping to control blood sugar levels. Research has indicated that obesity is a common problem among type 2 diabetic patients, contributing to insulin resistance. Engaging in regular physical activity and consuming a balanced diet to maintain a healthy weight can enhance tissue responsiveness to insulin, thereby improving the body's capacity to efficiently use this hormone and assist in overall weight control. The combination of lifestyle changes and insulin therapy, when appropriate, can be a potent approach to managing diabetes and averting long-term complications [36].

OADs

Type 2 diabetes can be managed using various oral hypoglycemic agents in addition to insulin. These include metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT2) inhibitors. Each class of drugs operates through distinct mechanisms to reduce blood glucose levels. The selection of an appropriate medication depends on the patient's specific requirements, tolerance, and treatment response.

Sulfonylurea

Sulfonylureas function by attaching to specific channels in pancreatic beta cells, resulting in enhanced insulin release. Glipizide is commonly administered as a single dose or split into two doses, taken 30 min before breakfast, with dosages ranging from 2.5 mg to 10 mg. Glimepiride is typically taken once daily with breakfast or twice daily with meals, in doses of 1 mg, 2 mg, or 4 mg. For individuals at higher risk of hypoglycemia, such as elderly patients or those with renal impairment, the initial dose may be as low as 0.5 mg daily. Glyburide comes in 1.25 mg, 2.5 mg, or 5 mg tablets, which can be taken as a single dose or divided into two doses [37,38].

Meglitinides

Meglitinides operate by controlling adenosine triphosphate-sensitive potassium channels in pancreatic beta cells, leading to increased insulin secretion, similar to the mechanism of sulfonylureas. Repaglinide, a meglitinide, is available in 0.5 mg, 1 mg, or 2 mg tablets and is taken orally in two to three divided doses per day.

Metformin

Metformin is a commonly prescribed initial pharmacological treatment for managing T2DM. It functions by boosting the activity of hepatic AMP-activated protein kinase, which results in decreased hepatic gluconeogenesis and lipogenesis while enhancing insulin-stimulated glucose uptake in skeletal muscles. The typical oral administration of metformin involves divided doses of 500–1000 mg, taken twice daily. This medication has demonstrated effectiveness and good tolerability in patients with type 2 diabetes [39], contributing to improved glycaemic control and overall metabolic health [40].

Thiazolidinediones (TZDs)

These medications stimulate a nuclear receptor known as peroxisome proliferator-activated receptor gamma. This action improves insulin sensitivity, enhances glucose absorption by peripheral tissues, and elevates the levels of adiponectin, a fat-derived cytokine that further promotes insulin sensitivity and lipid metabolism. Pioglitazone is offered in daily doses of 15 mg, 30 mg, or 45 mg tablets. Although less frequently prescribed, rosiglitazone is administered in daily doses of 2 mg, 4 mg, or 8 mg [41,42].

Alpha-glucosidase inhibitors

This group of oral antidiabetic medications functions by competitively inhibiting the alpha-glucosidase enzymes found in the intestinal brush border cells. These enzymes play a crucial role in breaking down dietary starches and complex carbohydrates. By hindering this process, the absorption of polysaccharides and the conversion of sucrose into glucose and fructose are delayed. This results in a more gradual release of glucose into the bloodstream, effectively managing postprandial hyperglycemia. Alpha-glucosidase inhibitors come in various strengths and are typically administered 3 times a day, right before meals [43,44].

DPP-4 inhibitors

These medications function by inhibiting the enzyme DPP-4. This action prevents the deactivation of glucose-regulating hormones such as glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1. Consequently, DPP-4 inhibitors affect glucose control through various mechanisms, including decreasing glucagon secretion, boosting glucose-stimulated insulin release, decelerating gastric emptying, and promoting satiety.In the DPP-4 inhibitor class, linagliptin is administered as a 5 mg daily dose. Vildagliptin is prescribed as 50 mg once or twice weekly, sitagliptin as 25 mg, 50 mg, or 100 mg once daily, and saxagliptin as 2.5 mg or 5 mg once daily [45,46].

SGLT2 inhibitors

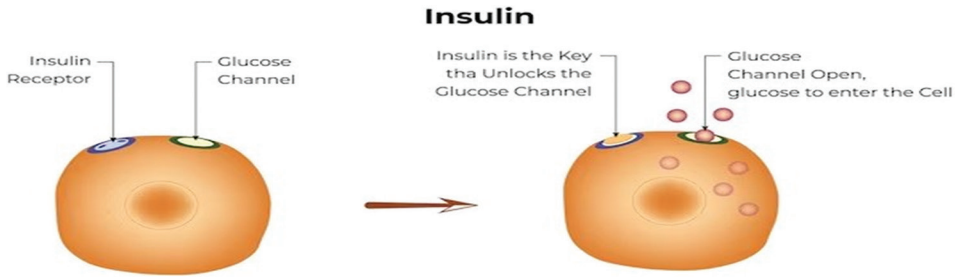
These are a class of medications, function by inhibiting the SGLT2 in the kidneys, specifically in the proximal renal tubules. This action results in decreased glucose reabsorption and increased glucose excretion in the urine, ultimately leading to a reduction in blood glucose levels in individuals with diabetes. The dosing regimens for these medications vary, with canagliflozin typically starting at 100 mg/day and potentially increasing to 300 mg/day. Dapagliflozin is often prescribed at a dose of 5 mg or 10 mg once daily, whereas empagliflozin is available in 10 mg or 25 mg daily doses. By reducing glucose reabsorption in the kidneys, these medications enhance urinary glucose excretion and improve blood sugar control. Furthermore, SGLT2 inhibitors offer additional benefits, including weight loss and blood pressure reduction, which can be particularly beneficial for individuals with type 2 diabetes. Research has shown that these medications can provide significant advantages in managing diabetes, as highlighted by studies such as those conducted by [47,48].

MECHANISM OF DRUGS: PATHWAYS OF ANTI DIABETIC MEDICATION

Drug mechanisms are intricate and diverse, encompassing numerous processes that influence how substances move, change, and ultimately affect the human body. A key component in comprehending these mechanisms is pharmacokinetics, which examines how drugs travel within the body. For drugs to reach their intended targets, they must first overcome biological obstacles, such as cell membranes [49]. A drug's ability to be absorbed, distributed, and reach its site of action is greatly influenced by its physicochemical characteristics, including pH and solubility [50]. After absorption and distribution, drugs may undergo metabolic alterations that modify their structure and activity. These biotransformation processes can either enhance or diminish a drug's effectiveness, depending on the specific reactions involved [51]. Comprehending the mechanisms of drug action is crucial for creating, improving, and safely administering pharmacological treatments.

INSULIN

As type 2 diabetes progresses, insulin therapy becomes essential for management. The evolution of insulin products has led to a wide array of options with unique characteristics, resulting in various treatment regimens. The goal of insulin replacement therapy is to replicate the function of pancreatic beta cells by providing both basal and prandial insulin. Intermediate-acting, long-acting, or ultra-long-acting insulin analogues can be used to achieve basal insulin levels. Despite the availability of OADs, insulin remains the most effective treatment, offering numerous benefits such as reducing glucotoxicity, inhibiting lipotoxicity, decreasing inflammation, eliminating reactive oxygen species, promoting beta-cell recovery, maintaining functionality, and enhancing insulin sensitivity. However, factors such as hypoglycemia risk, weight increase, injection-related fears, and practical difficulties may hinder its initiation. When non-insulin monotherapy fails to achieve or maintain target HbA1C levels, additional oral medications, glucagon-like polypeptide receptor agonists, or basal insulin may be introduced. Insulin therapy should be considered for newly diagnosed type 2 diabetes patients exhibiting symptoms such as weight loss, ketosis, or hyperglycemia, or those with extremely high blood glucose levels. This approach may also be recommended for patients who have not reached their glycemic targets [53]. Basal insulin is typically the initial insulin regimen, often added to oral metformin, along with a potential additional non-insulin medication such as a DPP-4 inhibitor or SGLT-2 inhibitor. NPH insulin is frequently used due to its low hypoglycemia risk and cost-effectiveness. If basal insulin controls fasting blood glucose but HbA1C remains elevated, mealtime insulin may be added. Rapid-acting insulin analogs can be administered before meals [54]. Inhaled insulin is an alternative option for prandial use, although its dosing range is limited. For patients with poor glucose control, particularly those requiring increasing insulin doses, TZDs or SGLT2 inhibitors may be combined with insulin therapy. Insulin can cause side effects such as weight fluctuations, electrolyte imbalances, and allergic reactions. The concurrent use of insulin and certain medications, like TZDs, may increase the risk of heart failure [55]. Weight gain is also a challenge associated with insulin use in type 2 diabetes. Previous studies have shown that oral medications can be effective even for newly diagnosed patients with high HbA1c, suggesting that oral therapies may be appropriate even when HbA1c is significantly elevated at diagnosis [56].



THE MECHANISM OF ACTION OF INSULIN

This process involves the attachment of insulin to particular cell surface receptors, initiating a series of intracellular signaling events that ultimately result in cellular glucose uptake and utilization [57,58]. A key characteristic of T2DM is insulin resistance, which occurs when target cells become less sensitive to insulin's effects. This can arise from various deficiencies in the insulin signalling pathway, including reduced tyrosine phosphorylation of the insulin receptor or its downstream substrates, as well as changes in the expression or function of glucose transporters such as GLUT4 [59]. Medications that can replicate insulin's effects or target specific components of it signalling pathway may offer therapeutic benefits for diabetes management.

SULFONYLUREA: GLIMEPIRIDE

Glimepiride, a sulfonylurea medication, is utilized to control blood glucose levels in individuals with type 2 diabetes. It can be prescribed alone or in conjunction with other OADs [1]. The FDA sanctioned glimepiride in 1995 for standalone use or combined therapy with metformin or insulin for type 2 diabetes management. Sweden was the first country to introduce it in clinical practice. When used alone, glimepiride can reduce HbA1c by 1.5–2%. As a third-generation sulfonylurea, glimepiride uniquely interacts with the sulfonylurea receptor 1, resulting in quick onset and dissociation. Beyond its pancreatic effects, glimepiride decreases insulin resistance and boosts glucose uptake through glucose transporter 4 [2].

Dosing information

The initial recommended glimepiride dose is 1–2 mg taken before the first meal of the day. Dosage adjustments are based on plasma glucose levels, with a typical maintenance range of 1–4 mg and a maximum daily dose of 8 mg [60].

Pharmacokinetics

Oral administration of glimepiride results in swift absorption, with full absorption occurring within an hour. The drug exhibits strong plasma protein binding and is primarily metabolized in the liver. Most of the drug is eliminated through urine. Glimepiride's pharmacological effects last up to 24 h [60].

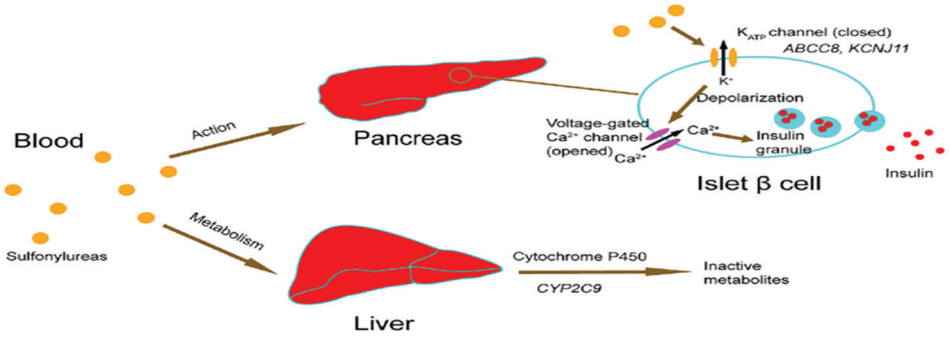
MECHANISM OF ACTION

The therapeutic effects of sulfonylureas are mediated by their interaction with ATP-sensitive potassium channels in the plasma membrane of pancreatic beta-cells, "Image source: [61]."

Glimepiride reduces blood sugar levels by promoting insulin release from pancreatic β-cells. It interacts with specific β-cell membrane receptors, leading to the closure of ATP-sensitive potassium channels [62]. Pancreatic effects: By inhibiting the ATP-sensitive potassium channel, glimepiride triggers β-cell membrane depolarization, facilitating calcium influx and subsequent insulin secretion. It also enhances β-cell glucose sensitivity, further boosting insulin release [63]. Extra-pancreatic effects: Glimepiride also improves peripheral tissue responsiveness to insulin, particularly in the liver and skeletal muscles. This is achieved through the activation and movement of the GLUT-4 glucose transport protein in fat and muscle tissues [1]. Some research suggests that glimepiride may have a more favourable impact on the cardiovascular system compared to other sulfonylureas [64].

Benefits of glimepiride

Although sulfonylureas are often linked to weight increase and low blood sugar, whereas glimepiride is well-tolerated and considered safe. It has a less risk of adverse effects than other sulfonylureas. However, the potential for such risks remains, and appropriate caution should be exercised when prescribing glimepiride to address these concerns [65]. Drug interactions: Lebovitz and Feinglos, 1978, noted several drug interactions, including the need to reduce glimepiride dosage when used alongside nonsteroidal anti-inflammatory drugs, aspirin, fibrates, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, selective serotonin reuptake inhibitors, antifungal agents, antibiotics, and certain anti-epileptic drugs. The risk of hypoglycemia increases when glimepiride is used concurrently with these agents. Cytochrome P450 2C9 (CYP2C9) metabolizes glimepiride; enzyme inducers such as rifampicin and inhibitors such as fluconazole can increase and decrease glimepiride metabolism, respectively. Therefore, glimepiride should not be administered with these drugs. Both short-term and long-term alcohol consumption can alter glimepiride's effects.



Contraindications and precautions

Glimepiride should not be used in patients with diabetic ketoacidosis, severe renal impairment, or severe hepatic impairment. Caution is advised for elderly patients, those with mild-to-moderate kidney impairment, and during pregnancy. The most frequent side effects of glimepiride include low blood sugar, weight gain, nausea, and diarrhoea. Glimepiride is often combined with metformin for managing type 2 diabetes.

BIGUANIDES: METFORMIN

French scientists initially uncovered the glucose-lowering effects of metformin in the 1950s. Although less potent than other biguanides, metformin stands as the only drug in this class that rarely induces the hazardous side effect of lactic acidosis. Both the American and European Diabetes Associations strongly endorse metformin as the primary pharmacological treatment for type 2 diabetes management, in conjunction with lifestyle changes and exercise. Metformin is widely regarded as a safe and efficacious antidiabetic medication, suitable for use alone or with other diabetes treatments [66]. While its precise mode of action remains unclear, recent research indicates that metformin may improve insulin receptor binding and amplify insulin's bodily effects. Metformin's antidiabetic action primarily stems from its ability to decrease glucose production in the liver, resulting in lower fasting and post-meal blood glucose levels [67].

Dosage options

Metformin comes in 500 mg and 850 mg tablet forms. The standard starting dose is 500 mg, administered 2 or 3 times/day. Alternatively, doctors may prescribe 850 mg once or twice daily. If necessary, the metformin dose can be increased to a maximum of 2,000 mg daily, with any dose implemented gradually [53]. The small intestine absorbs about 50–60% of the administered metformin. As the metformin dose increases, the absorption rate decreases. Metformin distributes well throughout the body's compartments but does not bind to plasma proteins or undergo liver metabolism. Instead, the kidneys excreted it unchanged [68].

MECHANISM OF ACTION

Systemic effects of metformin (Image source: Zhang *et al*., 2023).

The complete mechanism of metformin's action remains unclear, but current evidence indicates that it functions by decreasing glucose production in the liver and enhancing glucose uptake and use in peripheral tissues [69]. Metformin inhibits the mitochondrial respiratory chain complex I, reducing ATP formation and activating the AMP-activated protein kinase pathway, which leads to decreased hepatic gluconeogenesis. It also suppresses gluconeogenic gene expression and reduces intestinal glucose absorption [2,70]. Furthermore, metformin enhances insulin sensitivity and glucose uptake in peripheral tissues, potentially by increasing glucose transporter 4 expression and translocation, and boosting glycolysis. It also inhibits fatty acid oxidation and reduces fat accumulation in the liver and peripheral tissues, contributing to improved insulin sensitivity [71]. Long-term use of metformin is generally considered weight-neutral and does not increase hypoglycemia risk. It has been shown to reduce appetite and decrease carbohydrate absorption in the intestines, while also inhibiting liver gluconeogenesis and promoting glucose utilization in peripheral tissues. Although metformin is regarded as one of the safest antidiabetic medications due to its glucose-lowering mechanism not involving insulin secretion stimulation from pancreatic β cells, it can cause lactic acidosis, a rare but serious side effect. This condition can be exacerbated by alcohol consumption and has a mortality rate of up to 50%. Metformin may also cause mild gastrointestinal issues such as nausea and diarrhea, and can interfere with vitamin B12 absorption [66].

Contraindications

Metformin should be avoided in patients with congestive heart failure, chronic obstructive pulmonary disease, severe infections, or gangrene. It is also contraindicated for individuals with liver disease, kidney impairment, advanced age, dehydration, sepsis, or excessive alcohol intake. While generally well-tolerated, metformin commonly causes gastrointestinal side effects such as diarrhea, nausea, vomiting, and abdominal discomfort [72].

Drug interactions

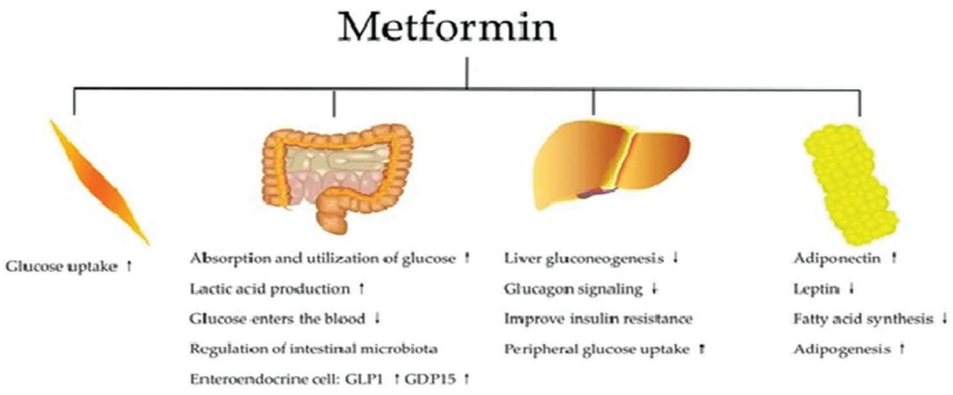
Cimetidine and furosemide inhibit metformin excretion, leading to its toxicity. Glucocorticoids, thiazide diuretics, phenothiazines, nicotinic acid, and calcium channel blockers may counteract the hypoglycemic effect of metformin [66].

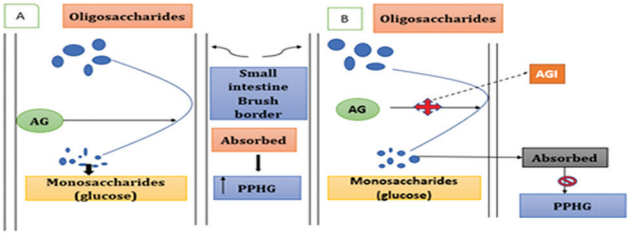
ALPHA GLUCOSIDASE INHIBITOR: VOGLIBOSE

Voglibose, a medication first identified in Japan in 1981, has been utilized to manage T2DM since 1994. This α-glucosidase inhibitor functions by impeding the alpha-glucosidase enzyme, thereby slowing glucose absorption and reducing post-meal blood glucose levels. For type 2 diabetic patients experiencing elevated glucose levels after meals, especially those who have not achieved optimal control with other antidiabetic medications, voglibose is highly recommended as an antihyperglycemic agent. Research indicates that voglibose not only controls postprandial glucose but also offers cardiovascular protection by enhancing oxidative stress and endothelial function, which are known contributors to heart disease [73]. Specifically, voglibose has been found to positively affect oxidative stress markers, decreasing reactive oxygen species and boosting antioxidant defenses. Moreover, voglibose has shown the capacity to enhance endothelial function, potentially improving cardiovascular health and blood flow. These protective effects on the heart make voglibose a valuable treatment option for patients with type 2 diabetes, particularly those at increased risk of cardiovascular complications [74].

MECHANISM OF ACTION

The first section describes how α-glucosidase enzyme converts oligosaccharides into monosaccharides, leading to increased





postprandial glucose levels. The second part explains that α-glucosidase inhibitors prevent this conversion, thereby reducing postprandial hyperglycemia. Image source: Kumar *et al.*, 2018. Voglibose, an antidiabetic medication classified as an alpha-glucosidase inhibitor, functions by competitively blocking intestinal alpha-glucosidase enzymes [58,74]. These enzymes are crucial for the breakdown of complex carbohydrates into absorbable monosaccharides, such as glucose. By hindering this digestive process, voglibose slows carbohydrate absorption, consequently lowering postprandial hyperglycemia in type 2 diabetes patients [58,74]. This treatment approach is especially advantageous for individuals with type 2 diabetes struggling to maintain proper glycemic control, as it results in decreased postprandial blood glucose levels [58].

Dosage information

The suggested starting dose of voglibose is 0.2 mg taken with meals. If the desired glycemic response is not achieved, the dose may be carefully increased. Voglibose is typically administered alongside dietary changes or in combination with other oral hypoglycemic drugs. Moreover, voglibose has poor gastrointestinal absorption, undergoes liver metabolism, and is eliminated through urine [75].

Drug interactions

Taking voglibose simultaneously with insulin or other antidiabetic medications may increase the risk of hypoglycemia, necessitating close monitoring and dose adjustments. Furthermore, hypoglycemia can occur when voglibose is used in conjunction with medications that enhance the hypoglycemic effects of antidiabetic agents, such as beta-blockers, salicylates, monoamine oxidase inhibitors, and fibrates [76].

DPP4 INHIBITORS: TENELIGLIPTIN

Teneligliptin, a novel DPP-4 inhibitor known for its high potency and selectivity, was initially sanctioned for type 2 diabetes treatment in Japan in 2012, followed by approvals in Korea and India. Although structurally distinct, all DPP-4 inhibitors operate via a shared mechanism. Notably, teneligliptin demonstrates five-fold greater efficacy compared to sitagliptin. The American Diabetes Association endorses DPP-4 inhibitors, including teneligliptin, for single-, dual-, and triple-drug therapies in conjunction with other antidiabetic medications such as sulfonylureas, biguanides, TZDs, or insulin [58]. Teneligliptin is commonly prescribed when lifestyle modifications and combinations of diet, exercise, and either sulfonylureas or TZDs fail to adequately control blood glucose in type 2 diabetes patients. It is taken orally, starting at 20 mg/day, with a maximum dose of 40 mg/day. Clinical trials have confirmed its efficacy and safety [77]. In T2DM, elevated blood glucose can trigger oxidative stress, potentially leading to cardiovascular endothelial dysfunction. Teneligliptin has been found to enhance endothelial function through its antioxidant, anti-inflammatory, and anti-thrombotic effects, as well as its ability to neutralize hydroxyl radicals. By influencing these pathways, teneligliptin can help reduce the adverse cardiovascular effects associated with chronic hyperglycemia in type 2 diabetes [58]. Furthermore, teneligliptin has shown positive effects on lipid metabolism. Research has indicated that administering teneligliptin before breakfast results in prolonged postprandial blood glucose reduction throughout the day, with comparable effects observed after the evening meal [77]. In addition to its glycemic benefits, teneligliptin has exhibited non-glycemic advantages, such as improving lipid profiles and decreasing indicators of renal and hepatic dysfunction in type 2 diabetes patients [78].

MECHANISM OF ACTION:

Teneligliptin DPP4 inhibitor mechanism of action. Image source: Ahrén *et al.*, 2016.

Incretin hormones, specifically glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide, are produced by enteroendocrine cells and are essential for blood sugar regulation through their stimulation of insulin release from pancreatic beta cells. These hormones have a brief lifespan due to rapid inactivation by DPP-4, leading to increased blood glucose levels. DPP-4 inhibitors, such as teneligliptin, extend the active period of incretins by inhibiting the DPP-4 enzyme, thereby enhancing insulin secretion and improving glycemic control in type 2 diabetes patients [7].

Medication interactions

The blood sugar-lowering effect of teneligliptin may be diminished when used alongside corticosteroids. Furthermore, administering teneligliptin with quinidine sulfate hydrate, amiodarone hydrochloride, or sotalol hydrochloride could potentially cause QT prolongation. Teneligliptin, an oral medication, reaches its maximum concentration in about 1 h and has a half-life of approximately 18.9 h. The drug's

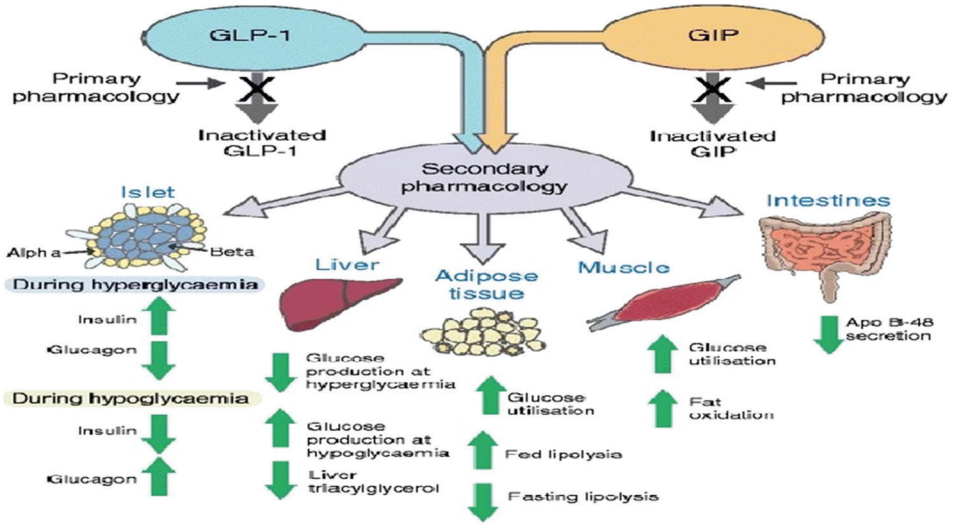


Table 1: Overview of oral antidiabetic drugs and insulin: Mechanisms, effects, administration, and toxicities

OADs and subclass	Mechanism of action	Effects	Route of administration half-life and toxicities
Insulins Fast-acting/Quick-acting Regular insulin Medium-duration insulin Extended-release insulins	Trigger insulin receptor	Reduce circulating glucose	Parenteral, duration varies Toxicity: low blood sugar, increased weightand in rare cases, abnormal fat distribution under the skin
Sulfonylureas • Glipizide, Glyburide, Glimepiride, Gliclazide	Close K+ channels in betacells	Reduce circulating glucose inpatients with functioning betacells	Oral, active duration 10–24 h Toxicity: Hypoglycemia, weight gain
Meglitinide analogues D-Phenylalanine derivative • Repaglinide, Nateglinide	Like sulfonylureas with some overlap in binding sites	Reduce circulating glucose inpatients with functioning betacells	Oral, very fast onset of action, duration5–8 h, Nateglinide< 4h Toxicity: Hypoglycemia
Biguanides • Metformin	Activates AMP kinase and reduces hepatic and renal gluconeogenesis	Decreases circulating glucose	Oral, maximal plasma concentration in 2–3 h Toxicity: Gastrointestinal symptoms, lactic acidosis (rare)
Alpha-Glucosidase Inhibitors • Acarbose, miglitol • Voglibose1	Inhibit intestinal α-glucosidases	Reduce conversion of starchand disaccharides to Monosaccharides	Oral, rapid onset Toxicity: Gastrointestinal symptoms
Thiazolidinediones Pioglitazone, Rosiglitazone	Regulate gene expression by binding to PPAR-γ and PPAR-α	Reduce insulin resistance	Oral, long acting (>24 h) Toxicity: Fluid retention, oedema, anaemia, weight gain, macular oedema, bone fractures
Glucagon-like polypeptide-1 (GLP-1) receptor agonists Exenatide, Liraglutide, Albiglutide, Dulaglutide	Analog of GLP-1: Binds to GLP-1 receptors	Increase glucose mediated insulin release, lower glucagon levels, slow gastric emptying, decrease appetite	Parenteral (SC) *Toxicity*: Nausea, headache, vomiting, anorexia, mild weight loss, pancreatitis, C-cell tumours inrodents
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Sitagliptin, Saxagliptin, Linagliptin, Alogliptin, Vildagliptin	Blocks degradation of GLP-1, raises circulating GLP-1 levels	Increases glucose mediated insulin release, lowers glucagon levels, slows gastric emptying, decreases appetite	Oral, half-life ~12–24 h *Toxicity*: Rhinitis, upper respiratory infections, headaches, pancreatitis, rare allergic reactions
Sodium-glucose co-transporter 2 (SGLT-2) inhibitors Canagliflozin, Dapagliflozin, Empagliflozin	Block renal glucose resorption	Increase glucosuria, lower plasma glucose levels	Oral, half-life ~10–14 h *Toxicity*: Genital and urinary tract infections, polyuria, pruritus, thirst, osmotic diuresis, constipation

metabolism and elimination occur through both hepatic and renal pathways. Due to these specific pharmacokinetic properties, patients with type 2 diabetes who have kidney or liver impairment do not require dose adjustments for teneligliptin [7].

Contraindications

Teneligliptin should not be used in patients allergic to any DPP-4 inhibitors. It is also contraindicated in cases of diabetic ketoacidosis, diabetic coma or precoma, severe trauma, situations requiring insulin injection for blood sugar control, and in individuals with prolonged QT intervals [76]. While teneligliptin is generally well-tolerated, it may occasionally cause constipation and hypoglycemia. The safety profile of DPP-4 inhibitors is similar across the class. Hypoglycemia occurs more frequently when teneligliptin is combined with other antihyperglycemic medications compared to its use as a single agent. Frequently reported side effects include nasopharyngitis, upper respiratory tract infection, hyperkalemia, arthralgia, and back pain. Rare but serious adverse events such as acute pancreatitis, severe hypersensitivity reactions, and severe skin reactions have been documented in clinical studies [2].

Pros and cons of prolonged OAD usage in different aspects

Research has demonstrated that consistent, long-term use of oral antidiabetic medications offers substantial advantages for diabetic patients. These drugs play a is essential role in diabetes management and the prevention or delay of chronic complications [34]. Research indicates that a large proportion of diabetics utilizing traditional hypoglycaemic plant-based remedies experienced positive outcomes, including better glycaemic control and symptom alleviation, with most reporting no adverse effects [78]. Furthermore, specific types of oral antihyperglycemic medications have been shown to enhance glucose metabolism and contribute to the overall treatment strategy for T2DM patients [44]. Although oral antidiabetic medications can effectively control diabetes, their extended use may lead to potential complications. Research has linked some of these drugs to various severe side effects, which can complicate the long-term treatment of the disease [76]. Additionally, as diabetes progresses, patients may require increased drug dosages and the incorporation of other oral medications or insulin to maintain target blood sugar levels, potentially elevating the risk of adverse reactions [44]. Studies in ethnobotany indicate that numerous plants exhibit antidiabetic properties, highlighting that the development of widely prescribed hypoglycemic medications, such as metformin, originated from traditional medicinal practices. In conclusion, the administration of OADs necessitates a delicate equilibrium between their therapeutic benefits and possible negative consequences, especially when considering long-term usage. Extended use of oral medications for diabetes can result in the onset of long-term complications, including kidney disease, nerve damage, eye problems, heart disease, and blood vessel issues in the extremities, causing harm to various tissues. Managing these complications can be expensive and may necessitate more intensive treatment approaches, potentially increasing the likelihood of side effects [52]. In the end, the choice to utilize oral diabetes medications, especially for extended periods, should be approached with caution. It is essential to weigh the potential advantages against the possible disadvantages and to seek guidance from a medical professional before treatment planning.

EFFICACY OF PROLONGED OAD TREATMENT

Although oral antidiabetic medications can initially be successful in controlling diabetes, their effectiveness may decrease over time. As diabetes advances, it may become necessary to increase drug dosages or incorporate additional types of oral medications or insulin to maintain the desired blood sugar levels [44]. This approach, however, can lead to an increased likelihood of side effects and a reduction in the overall efficacy of the treatment. Moreover, research has indicated that certain OADs may cause a range of serious adverse reactions, potentially complicating their long-term usage [77]. The administration of oral antidiabetic medications is a nuanced and intricate matter, involving careful consideration of both potential advantages and disadvantages.

SAFETY CONSIDERATIONS IN PROLONGED OAD THERAPY

Extended use of oral antidiabetic medications can pose additional safety risks beyond the previously mentioned drawbacks. Adverse effect of this drug, including hypoglycemia, digestive problems, and heart-related issues [44,78]. Prolonged usage may elevate the likelihood of experiencing these adverse reactions, potentially resulting in more severe health outcomes. When prescribing OADs for extended periods, it is essential to closely monitor and address these side effects. Moreover, long-term exposure to these medications may increase the risk of developing complications. Healthcare providers must carefully weigh the advantages of blood sugar control against the potential hazards associated with prolonged use. Striking the right balance is crucial for optimal patient care.

IMPROVED GLYCAEMIC CONTROL WITH PROLONGED OADs

Extended use of oral antidiabetic medications offers a key advantage: the possibility of enhanced blood sugar management. These drugs can effectively reduce glucose levels in the blood, which is essential for diabetes control and for preventing or postponing the development of long-term health issues. Research indicates that strict glycemic control, regardless of the specific medication used, can reduce the occurrence of small blood vessel complications, including damage to the eyes, kidneys, and nerves [44]. Nevertheless, as diabetes progresses, these medications may become less effective, potentially requiring higher doses or the addition of other oral agents or insulin to reach the desired blood sugar target.

POTENTIAL ADVERSE EFFECTS OF PROLONGED OAD USE

Although oral antidiabetic medications can be beneficial in diabetes management, their prolonged use may lead to various unwanted effects. Some of these drugs have been associated with a higher risk of low blood sugar, which can be particularly dangerous for patients with advanced complications or reduced ability to recognize hypoglycemia. Furthermore, extended use of certain OADs has been linked to digestive problems, such as nausea and difficulty passing stools, as well as potential heart-related issues. These adverse reactions of drugs and quality of life had linear association and may necessitate additional treatments to address.

CONCLUSION

Long-term use of diabetes medications has yielded mixed results in managing type 2 diabetes (all those effects were represented in Table 1). Metformin is a preferred initial treatment due to its effectiveness, safety, and affordability. However, it can cause stomach issues and requires caution in patients prone to lactic acidosis. Other options, like sulphonylureas, can lower blood sugar but often lead to weight gain and low blood sugar levels. TZDs, on the other hand, have shown potential to increase the risk of cardiovascular disease, limiting their widespread use. The more recently developed class of drugs, DPP-4 inhibitors, has shown promising results in terms of efficacy and safety. Sitagliptin, a DPP-4 inhibitor, has been found to be equally effective as other anti-diabetic agents with a favourable adverse effect profile. In contrast to the chemical and biochemical agents, natural medicines, particularly certain Chinese herbal medicines, have also demonstrated antidiabetic properties and may be a viable alternative for patients concerned about the side effects of conventional drugs. It is a very important for the practitioners, diabetologist as well as patients to have the knowledge about benefits and side effects of their treatment protocol for diabetes, especially they must know about the complications of long-term usage of the oral anti diabetic drugs, which were included in their treatment plan. Overall, the long-term management of type 2 diabetes demands a balanced approach, weighing the efficacy, safety, and tolerability of available anti-diabetic medications, with a particular focus on mitigating long-term side effects associated with commonly prescribed oral anti-diabetic drugs to prevent potential harm.

AUTHOR CONTRIBUTION

All authors contributed equally.

CONFLICTS OF INTERESTS

Declared none.

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