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Oral Anti-Diabetic Agents-Review and Updates

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Authors' contributions

Author POO designed the study, participated in the literature search. Author EUO participated in designing the work and in searching the literature. Author PFU participated in designing the work, searched the literature and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Diabetes is a chronic metabolic disorder with high mortality rate and with defects in multiple biological systems. Two major types of diabetes are recognized, type 1 and 2 with type 2 diabetes (T2D) being by far the more prevalent type. As diabetes affects multiple biological functions, the use of multiple drug classes having different mode of actions is required in order to optimize therapy in diabetic patients. Five major classes of oral antidiabetic agents (OHA) have traditionally been used for the management of patients with T2D. These include the sulphonylureas, meglitinides, biguanides, thiazolidinediones and the alpha-glucosidase inhibitors. Several newer classes of agents have also been introduced recently in the pharmacotherapy of T2D, including the incretin mimetics, the dipeptidy peptidase 4 (DPP-4) inhibitors, the sodium glucose co-transporter 2 (SGLT 2) inhibitors and more recently, the dual peroxisome proliferator-activated receptor (PPAR) agonists. Each of these agents has been shown in various experimental and clinical settings to be efficacious in T2D, but each is also associated with a number of adverse effects. Despite the vast

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array of drugs introduced, metformin, a biguanide, largely remains the first choice mono therapy in T2D patients but several combination options are also available in poly pharmacy when mono therapy fails to produce the required glycemic control. The increasing number of drugs, together with numerous combination options in poly pharmacy, presents with the clinician an increasing complexity of therapeutic options. The likely pathogenetic mechanism of diabetes operating in the patient, as well as the mode of action, efficacy and safety of the drugs are some of the major considerations in the choice of any given agent or its combinations. This review therefore focuses on the mode of action, pharmacokinetics, indications, efficacy and adverse effects of the OHA used in T2D.

Keywords: Antidiabetic drugs; DPP-4 inhibitors; metformin; oral hypoglycemic agents (OHA); saroglitazar; SGLT 2 inhibitors; sulphonylureas.

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia resulting from inadequate insulin secretion, failure of insulin to elicit normal level of response in insulin sensitive tissue (insulin resistance), or both [1]. In 2011, there were 366 million people with DM worldwide, and this is expected to rise to 552 million by 2030 [2]. DM impacts more than 25 million people in the US and continues to rise in number due to obesity, decrease in physical activity and an aging population [3-5]. DM is not only the leading cause of kidney failure, non-traumatic lower-limb amputations, and blindness among adults in the US, but is also a major cause of cardiovascular (CV) disease and stroke, and is the seventh leading cause of death in the US [3,5]. The current (2012 estimate) global mortality rate of DM is 4.8 million deaths [6].

Two distinct types of DM are generally recognized, type 1 (T1D) and type 2 diabetes (T2D) with T2D accounting for about 90% of DM [7]. While genetics is a factor in both types of DM, T1D is caused mainly by immune destruction of the pancreatic beta-cells while obesity plays a major role in the pathogenesis of T2D [1].

Management of DM concentrates on keeping blood sugar levels as close to normal as possible without causing hypoglycemia. The main measure of glycemic control is glycosylated hemoglobin (HbA1c), which gives an overall indication of glycemic control over the previous 12 weeks [8,9]. In every type of DM, the goal of treatment is an HbA1c level of less than 6.5% or maintaining the normal fasting plasma glycemia of less than 100 mg/dl (6.1 mmol/L) [10]. This can usually be accomplished with diet, exercise, and use of appropriate medications (insulin in the case of T1D, essentially oral medications or with insulin in T2D). The oral antidiabetic agents (OHA) that have been used in T2D include the sulphonylureas (SU), meglitinides, biguanides, thiazolidinediones (TZD) and alpha-glucosidase inhibitors. Newer agents have been recently been added to the armamentarium of T2D pharmacological management. These include the incretins, glucagon-like peptide-1 (GLP-1) and their enzyme inhibitors-dipeptide peptidase -4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors and the dual peroxisome proliferator-activated receptor (PPAR) α and γ agonists. All except the GLP-1 are oral agents. Several articles have reviewed the existing and some of these newer classes of agents in the past [11-13]. In addition, bile-acid sequestrants (BAS) and bromocriptine as antidiabetic agents have been discussed elsewhere [14]. However, as newer drugs under these classes of T2D drugs become available in clinical practice, a review of the current role of the new agents as well as the existing ones in T2D becomes imperative. The present review provides an update on the existing and newer OHA on their mode of action, efficacy and safety. However, the GLP-1 agonists are not discussed in the present review as they are not orally administered presently.

Data were sourced by searching the Pub Med, Medline, Google scholar up to December 2013 using keywords such as anti diabetic drugs and oral hypoglycemic agents. Original and review articles which are related to the subject were selected.

2. SULPHONYLUREAS

These are agents possessing sulphonyl group linked to one of the two nitrogen atoms of urea Fig. 1A. Historically, the high incidence of hypoglycemia in typhoid patients treated with a bacteriostatic isopropylthiadiazole derivative of

sulfanilamide led to the introduction of the first members of this group of drugs, carbutamide and later, tolbutamide, in 1956 [1,15]. Newer agents followed latter. Agents in this group are classified into two: first generation (carbutamide, acetohexamide, chlorpropamide, tolbutamide, tolazamide) and more recently introduced and more potent second generation (glipizide, gliclazide, glibenclamide or glyburide, glibornuride, gliquidone, glisoxepide, glyclopyramide, glimepiride). The molecular structure of glibenclamide is shown in Fig. 1B.

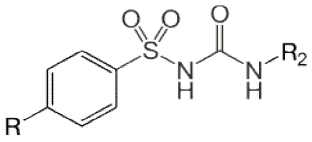


Fig. 1A. General structure of SU

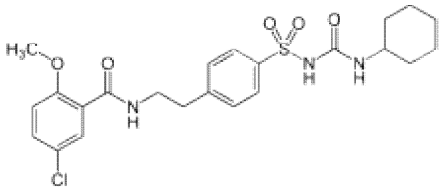


Fig. 1B. Chemical structure of glibenclamide

2.1 Mode of Action

Glucose is transported into the β-cells mainly by the non-insulin-dependent glucose transporter 2 (GLUT2), and the rate of glucose transport into the cell and metabolism reflect plasma glucose concentration. At low glucose concentrations, the trans-membrane potential of pancreatic β-cells is maintained at about -70 mV by an outward flow of K+ ions through the K_{ATP} channel. After a rise in plasma glucose, the increase in glucose metabolism leads to a rise in the ATP/ADP ratio, thus depolarizing the cell which leads to insulin release [1]. SU produce the same effect as plasma glucose rise. They have direct effects on the insulin- producing islet β-cells by blocking potassium current through the K_{ATP} channel. The K_{ATP} channel is an octameric complex of two protein subunits in a ratio of 4:4. One of the subunits, Kir6.2, is a member of the inward rectifying potassium channel family. The other regulatory subunit, SU receptor (SUR)-1, belongs to the ABC (ATP-binding cassette)-transporter superfamily. SU bind with the K_{ATP} channel at both a low affinity site on Kir6.2 and a high affinity site on SUR1 [1,13]. Binding of the SU closes these K_{ATP} channels; this reduces cellular potassium efflux thereby favoring membrane depolarization (the electric potential over the membrane becomes more positive). This depolarization opens voltage-dependent Ca^{2+} channels, resulting in an influx of Ca^{2+} that activates Ca^{2+}-dependent proteins. This leads to increased fusion of insulin granules with the cell membrane, and therefore increased secretion of (pro) insulin.

When SU bind with the K_{ATP} channel in the β-cell plasma membrane they cause prompt release of pre-formed insulin granules adjacent to the plasma membrane (first phase of insulin release). They also increase the extended phase (second phase) of insulin release that begins about 10 minutes later as insulin granules are translocated to the membrane from within the β-cell [16]. The protracted stimulation of the second phase of insulin release involves the secretion of newly formed insulin granules. The increased release of insulin continues while there is ongoing drug stimulation, provided the β-cells are fully functional. SU can cause hypoglycemia since insulin release is initiated even when glucose concentrations are below the normal threshold for glucose-stimulated insulin release; this threshold is approximately 5mmol/L [13].

2.2 Pharmacokinetics

They have excellent oral bioavailability being almost completely absorbed. The volume of distribution for the various SU are in the range of 0.1-0.3 L/kg, indicating limited distribution beyond extracellular water. They are highly bound to serum protein (90 -99%). The older first-generation SU are extensively metabolized and primarily excreted renally. The second generation agents are mostly metabolized by hydroxylation (with some active metabolites such as in glibenclamide) and eliminated mostly in urine, bile and feces [1].

2.3 Indications and Efficacy

SU are the first line oral drug for patients with T2D who have not achieved or maintained adequate glycemic control using non-pharmacological measures [13]. In terms of efficacy, clinical experience has shown that when used as monotherapy, they can be expected to reduce fasting blood glucose (FBG) by an average of 2–4 mmol/L accompanied by a decrease in HbA1c of 1–2% in patients inadequately controlled by non pharmacological measures [17]. SU require functional β-cells, so

they are useful in the early stages of T2D. They can be combined with metformin or with the TZDs.

2.4 Adverse Effects and Other Limitations

SU are generally well tolerated but they have certain limitations.

2.4.1 Hypoglycemia

This is the major adverse effect of the SU. Though usually subclinical or minor, they are occasionally life threatening [18]. The hypoglycemic episode can be mild in most cases but more severe hypoglycemia (requiring assistance or hospitalization), do occur in lesser cases. For instance, in 1998, the results of the randomized, 10-year multicenter studies, UK Prospective Diabetes Study (UKPDS) 33, [19], shows that about 20% of SU-treated patients reported one or more episodes suggestive of hypoglycemia annually. More severe hypoglycemia occurred in about 1% of SU-treated patients annually in the UKPDS. The mortality risk from severe SU-induced hypoglycemia was estimated at 0.014–0.033 per 1000 patient-years [18], while the incidence of hypoglycemia in insulin-treated patients were higher [20]. Patients with impaired hepatic or renal function risk severe hypoglycemia because of accumulation of active drug in circulation.

2.4.2 Weight gain

This is equally common with the SU therapy as with insulin. Typical range of weight gain in SU therapy is about 1-4 kg and this generally stabilizes after about 6 months. The anabolic effects of increased plasma insulin concentrations could possibly account for this [13].

2.4.3 Cardiovascular risk

Though there was an initial concern about the CV risk of the SU from the University Group Diabetes Program (UGDP) study in the 1970s which is a large US multicenter trial of antidiabetic therapy, the UKPDS showed no increase in cardiac events with SU treatment [21]. Recent studies have not found the benefit of these agents in cardiac patients. For instance, the ADVANCE trial (Action in Diabetes and Vascular Disease), a randomized trial sponsored by the vendor of gliclazide, found no benefit from tight control with gliclazide for the outcomes of heart attack (myocardial infarction), CV death, or all-cause death [22]. Similarly, ACCORD (Action to Control Cardiovascular Risk in Diabetes) [23] and the VADT (Veterans Affairs Diabetes Trial) [24] studies showed no reduction in heart attack or death in patients assigned to tight glucose control with various drugs. Thus, many authorities continue to advocate that SU use be kept to a minimum in patients with overt coronary artery disease [25] and all SU carry an FDA-required warning about increased risk of CV death.

2.4.4 Secondary failure and tachyphylaxis to SU

Secondary failure refers to the rapid and uncontrollable deterioration of blood glucose control during SU therapy. It occurs in approximately 5–10% of patients per annum with suggestions of differences in 'failure' rates between some compounds [26]. This phenomenon is common to all SU and is held to reflect an advanced stage of β-cell failure [13].

2.4.5 Loss of β-cells

Some diabetes experts feel that SU accelerate the loss of β-cells from the pancreas, and should be avoided [27].

2.4.6 Other adverse effects and warnings

- Dermatological (rash, purpura and pruritus), cholestatic jaundice especially with chlorpropamide and hyperinsulinemia;
- About 3% of patients experience gastrointestinal upsets;
- Bone marrow damage, although very rare, can be severe;
- Mild diuresis, particularly with tolazamide, acetohexamide and glyburide;
- Fluid retention and hyponatremia with chlorpropamide and, to a lesser extent, tolbutamide
- Use with caution in patients with hepatic dysfunction
- Fever, jaundice and blood dyscrasias are very rare;
- Photosensitivity has also been reported;
- Efficacy is still a problem: Kitzmiller [28] reported that among 73 women refusing insulin therapy who were assigned to receive glyburide, approximately 47% failed to achieve the targeted glycemic goals after 1 to 9 weeks of treatment. And in a US study of nongravid patients with T2D, 62% of those

treated with oral therapy failed to achieve the American Diabetes Association HbA1c goal of less than 7%. However, 73% of the patients treated with insulin also failed to achieve this threshold [29].

2.4.7 Drug interaction

They interact with a wide variety of other drugs which decrease (corticosteroids, isoniazide, oral contraceptives) or increase (aspirin and derivatives, allopurinol, sulfonamides etc.) the effect [13].

3. MEGLITINIDES (GLITINES)

These are rapidly acting oral blood glucose-lowering agents. Agents in this class are repaglinide, which gained FDA approval in 1997. Other drugs in this class include nateglinide and mitiglinide. Repaglinide consists structurally of the non-sulfonylurea moiety of glibenclamide and a salicylic acid derivative. Both salicylates and SU are known to reduce elevated plasma glucose levels, albeit by different mechanisms. Nateglinide is a derivative of the amino acid, D-phenylalanine, related somewhat to repaglinide. Their chemical structures are shown in Fig. 2.

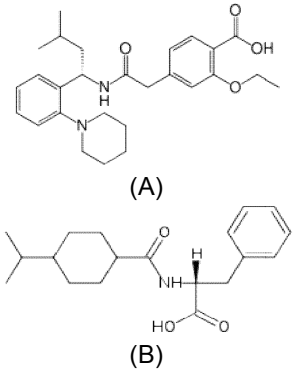


Fig. 2. Chemical structures of repaglinide (A) and nateglinide (B)

3.1 Mode of Action

They bind to an ATP-dependent K^+ (K_{ATP}) channel on the cell membrane of pancreatic β-cells in a similar manner to SU [1] but have a weaker binding affinity and faster dissociation from the SUR-1 binding site. This increases the concentration of intracellular potassium which causes depolarization and opening of the voltage-gated Ca^{2+} channels. The increased intracellular Ca^{2+} leads to the release of (pro) insulin as described earlier.

3.2 Pharmacokinetics

Repaglinide is rapidly and almost completely absorbed after oral administration with a very fast onset of action. The peak effect occurs about 1 hour after ingestion, but the duration of action is 5–8 hours. It is rapidly metabolized in the liver by CYP3A4 to inactive metabolites with a plasma half-life of 1 hour. About 90% repaglinide is recovered in the feces and approximately 8% in the urine. Nateglinide is absorbed faster than repaglinide with peak effect of less than 1 hour and elimination half life of approximately 3 hours.

Because of their rapid effect, these drugs are normally taken 15-30 minutes before a meal to restore the first phase of insulin release (which is lacking in T2D) and lower the postprandial hyperglycemia. Hypoglycemia is a risk if the meal is delayed or skipped or contains inadequate carbohydrate [13].

3.3 Indications and Efficacy

Meglinides, like the SU, are the mainstay in the treatment of T2D in patients with good β-cell function. The pharmacologic actions of these drugs are largely, if not entirely, mediated by increased insulin production, and thus are essentially the same as insulin [1]. Similar to SU, they typically reduce FBG by 3.3-3.9 mmol/L and HbA1c by 1.5-2% [21].

Meglinitides have several desirable properties including a rapid onset and short duration of action and metabolism, and excretion by non-renal routes. Furthermore, they can work synergistically with other antidiabetic drugs such as metformin in patients whose hyperglycemia is not controlled by monotherapy. Thus the meglitinides may offer some advantages in therapy over traditional and even newer antidiabetic drug therapies.

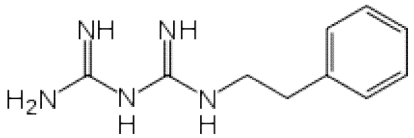
3.4 Adverse Effect and Limitations

- Hypoglycemia is a concern in the use of these drugs though this effect is lower than with SU since their effects are of shorter duration. In year-long pre-approval clinical trials with repaglinide, 13% of patients discontinued the use of the drug because of adverse events, most commonly hyperglycemia or hypoglycemia. In studies of 6 months or longer with nateglinide, 0.3% of patients discontinued because of hypoglycemia [1].

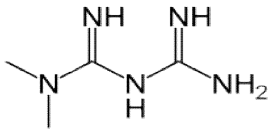
- These drugs are appreciably more expensive than most SU,
- Sensitivity reactions, usually transient, can occur;
- A small increase in weight could be expected in patients starting repaglinide as initial monotherapy. Nateglinide appears to have little effect on bodyweight when combined with metformin [30].

4. BIGUANIDES

In the 1920s, guanidine compounds were discovered in the extracts of *Galega officinalis* (French lilac) which is a plant used in Europe in the traditional management of diabetes for years. These compounds were too toxic to be used clinically but structural modifications led to drugs such as phenformin Fig. 3A, buformin and metformin Fig. 3B. Phenformin and buformin have been withdrawn from the market because of toxicity. Metformin was introduced to the United Kingdom in 1958, Canada in 1972, and the United States in 1995 and has a much better safety profile than the others. It is currently the principal biguanide drug used in diabetic pharmacotherapy worldwide.



(A)



(B)

Fig. 3. Chemical structure of phenformin (A) and metformin (B)

4.1 Mode of Action

Metformin has a variety of metabolic effects but the inhibition of hepatic glucose production is regarded as the principal mechanism through which metformin lowers blood glucose. It lowers blood glucose levels in T2D by suppressing hepatic glucose output (reduced gluconeogenesis) and increasing insulin-stimulated glycogen synthesis (or reduced glycogenolysis). Metformin and other biguanides may antagonize the action of glucagon, thus reducing FBG [31].

Besides suppressing hepatic glucose production, metformin improves insulin sensitivity by facilitating glucose transport across membranes (by inducing the phosphorylation of GLUT4 enhancer factor), and peripheral glucose uptake particularly in skeletal muscle. Metformin improves insulin sensitivity by reducing basal insulin concentration in hyperinsulinemic patients [13]. In addition, the drug causes a reduction of intestinal glucose absorption and reduces low-density (LDL) and very low-density lipoproteins (VLDL). A lowering of trigyceride and free fatty acids is suggestive of cardio-protective effect of the drug and is likely to help improve insulin sensitivity [1].

There are evidences that metformin exerts its actions through the activation of AMP-activated protein kinase (adenosine 5′-monophosphate-activated protein kinase, AMPK), an enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats [32]. Through phosphorylation of key proteins, AMPK acts as a regulator of glucose and lipid metabolism and cellular energy regulation [33]. It is suggested that metformin increases the amount of cytosolic AMP (as opposed to a change in total AMP or total AMP/ATP) [34]. Metformin is regarded as an antidiabetic (as opposed to hypoglycemic) agent in its mode of action. Metformin enhances insulin sensitivity but it is not effective in the absence of insulin; hence the drug is regarded as an 'insulin sensitizer'.

4.2 Pharmacokinetics

Metformin is hydrophilic and is slowly and incompletely absorbed with 20-30% recovered in feces. Food delays and reduces the extent of absorption. There is little binding of metformin to plasma proteins but it appears to accumulate in the red blood cells. The drug is not metabolized but excreted unchanged by tubular secretion (and some filtration) with an elimination half-life of about 6.2 hours [1,13].

4.3 Indication and Efficacy

Metformin is the therapy of choice for overweight and obese patients with T2D but also effective in normal weight patients. The outcome of the UKPDS coupled with extensive clinical experience with metformin have shown that the drug is efficacious. Long time administration has similar blood glucose reduction as the SU:

lowering plasma glucose by 2–4 mmol/L, corresponding to a decrease in HbA1c by approximately 1–2% [35].

The major merit of metformin that marks it as a first line monotherapy in T2D patients is that it is unlikely to cause severe hypoglycemia as it does not stimulate insulin secretion. The drug equally reduces insulin resistance by improving insulin sensitivity. Other advantages are that body weight tends to stabilize or reduce slightly during therapy with metformin (as opposed to weight gain with the insulin releasers). Over the 10-year treatment period in the UKDPS, the metformin group gained about 1 kg, the same as the dietary advice group, while the SU group gained 3 kg, and the insulin group, 6 kg [36,37]. Metformin also prevents the CV complications of diabetes. In the UKPDS, overweight patients who started oral antidiabetic therapy with metformin showed significant 39% reduced risk of myocardial infarction compared with conventional treatment [36]. It seems to reduce the progression of prediabetes to diabetes. In the US Diabetes Prevention Program, metformin reduced the incidence of new cases of diabetes in overweight and obese patients with impaired glucose tolerance by 33% overall as compared to intensive regimen of exercise and diet which reduced the risk by 58% [38]. However, it is unclear whether metformin slowed down the progression of prediabetes to diabetes simply due to its glucose-lowering action (treatment effect) [39]. In addition to the above merits, metformin remains one of the least expensive of the oral hypoglycemic agents and currently one of the two oral hypoglycemic agents (the other is gliclazide) included in the 2013 WHO Essential Drug List [40] which lists the most efficacious, safe and cost-effective minimum medicine needs for a basic health-care system. Metformin is believed to have become the most widely prescribed antidiabetic drug in the world [41].

The drug is available alone and in combination with other classes of oral hypoglycemic agents such as the SU (usually glibenclamide), TZDs (e.g. rosiglitazone). Metformin can also be used together with insulin. The safety data for the combination of metformin and SU has been reassuring [13]. The maximum daily dose of metformin is 2550 or 3000 mg.

Besides the use of metformin in T2D, the drug is increasingly being used, though still experimental, in polycystic ovary syndrome (PCOS) [42], non-alcoholic fatty liver disease (NAFLD) [43] and premature puberty [44], three other diseases that feature insulin resistance. A study has suggested metformin may somewhat reduce the incidence of pancreatic cancer [45,46] but this requires confirmation [47].

4.4 Adverse Effects and Other Limitations

4.4.1 Gastrointestinal effects

The major side effects associated with metformin therapy are gastrointestinal, including diarrhea, nausea, abdominal discomfort, and anorexia, which improve with dose reduction and can be minimized by slow dose titration. However, about 10% of patients cannot tolerate the drug even at lower dosage [13].

4.4.2 Lactic acidosis

The occurrence of lactic acidosis with metformin is rare (about 0.03 cases per 1000 patient-years), but the mortality rate is high. Phenformin was withdrawn in many countries in the 1970s because of a high incidence of lactic acidosis (rate of 0.40-0.64 per 1000 patient-years) [48]. Symptoms of lactic acidosis include hyperventilation, malaise and abdominal discomfort [13]. Common causes of increased lactic acid production include alcoholism (due to depletion of NAD+ stores), heart failure, and respiratory disease (due to inadequate oxygenation of tissues); the most common cause of impaired lactic acid excretion is kidney disease [49]. With metformin, lactic acidosis most often occurs in patients with renal insufficiency, or liver insufficiency, problems with alcohol abuse, or liver and cardiopulmonary disease [1].

4.4.3 Accumulation of drug in renal failure

Since the drug is eliminated as unchanged drug in the kidney, renal failure could lead to the accumulation of the drug.

4.4.4 Interference with vitamin absorption

Long-term use of metformin may interfere with absorption of vitamin B_{12} and folic acid; this may produce deficiency of these vitamins.

4.4.5 Other side effects

Other side effects include:

- Long term use is also associated with increased homocysteine levels

- Metallic taste has been reported.
- Metformin has been reported to decrease the blood levels of thyroid-stimulating hormone in people with hypothyroidism. The clinical implication of this is unclear [50].
- Therapy with metformin requires high doses with frequent daily administration; this is of less convenience to the patient and does not encourage compliance.

4.4.6 Drug interactions

Cationic drugs that are eliminated by tubular secretion may compete with metformin for elimination and this may result in clinically significant interactions. For example, cimetidine competes with metformin for elimination, resulting in increased serum concentrations of metformin. A small double-blind, randomized study found the antibiotic cephalexin also increases metformin concentrations by a similar mechanism [51]. Theoretically, other cationic medications may produce the same effect.

5. THIAZOLIDINEDIONES

These are also known as the 'glitazones'. They were introduced in 1990s. Chemically, the members of this class are derivatives of the parent compound, TZD Fig. 4A; they include: ciglitazone, troglitazone, rosiglitazone and pioglitazone. Ciglitazone was the prototype of this class of drugs but was withdrawn because of low potency and the appearance of cataracts in animals receiving long-term exposure to the drug. Troglitazone was introduced in the market in 1997 and withdrawn in 2000 due to an increased incidence of drug-induced hepatitis. Rosiglitazone was first released in 1999, but sales declined after the drug was found to increase risk of heart attack. The drug was withdrawn from the market in Europe (September 2010) and New Zealand (April 2011) [52], banned in India (2010) [53] and was put under selling restrictions in the US. Pioglitazone Fig. 4B was the tenth-best selling drug in the U.S. in 2008, with sales exceeding $2.4 billion [54]. Its CV safety profile compares favorably with rosiglitazone which has been banned in some countries. France and Germany have suspended the sale of pioglitazone and it has been withdrawn in some countries after a study suggested the drug could raise the risk of bladder cancer [55].

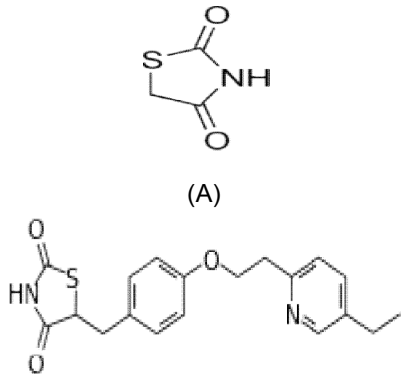


Fig. 4. The chemical structure of TZD (general structure, A) and pioglitazone (B)

5.1 Mode of Action

The major mechanism of action of these drugs is through the activation of the receptor, peroxisome proliferator-activated receptor (PPAR)γ. PPARγ is a member of the PPAR family of nuclear receptors, which are ligand-activated transcription factors regulating storage and metabolism of fatty acids. PPARs are expressed in fat cells, cells of the liver, muscle, heart, and inner wall (endothelium) and smooth muscle of blood vessels. PPARγ is expressed mainly in fat tissue, where it regulates genes involved in fat cell (adipocyte) differentiation, fatty acid uptake and storage, and glucose uptake. PPARγ operates in association with retinoid factor (RXR) to form the heterodimer which binds to nuclear response elements [13, 56]. The endogenous ligands for these receptors are free fatty acids (FFAs) and eicosanoids. Activation of the receptor by the ligand or TZDs modulates the transcription of a range of insulin-sensitive genes (lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid-binding protein, GLUT-4, phosphoenolpyruvate carboxykinase, malic enzyme and others) in the presence of necessary cofactors [57]. This leads to decreased gluconeogenesis and improved insulin sensitivity.

Reductions in plasma insulin concentrations and lowering of circulating triglycerides (TG) are additional mechanism for their actions. TZDs also promote amiloride-sensitive sodium ion reabsorption in renal collecting ducts, explaining the adverse effect of fluid retention [57]. TZDs, like metformin are antihyperglycemic agents and

are also regarded as 'insulin sensitizers' as they improve insulin sensitivity.

5.2 Pharmacokinetics

Both rosiglitazone and pioglitazone are rapidly and nearly completely absorbed, with time to peak plasma concentration of less than 2 hours. Absorption is slightly delayed by food. Both are highly (>99%) bound to plasma proteins with volume of distribution of 17.6 L for rosiglitazone and a single dose volume of distribution of 0.63 L/kg for pioglitazone. Both are subject to hepatic metabolism and both have a short (< 7 hours) elimination half-life for the parent drug, but substantially longer for the metabolites. The metabolites of rosiglitazone are eliminated mainly in urine and feces, and those of pioglitazone mainly in the bile [1].

5.3 Indications and Efficacy

These drugs are indicated in T2D especially in those (obese or non-obese) whose diabetes is not adequately controlled by diet and exercise. They can be used in monotherapy or in combination with other antidiabetic agents. The effect is slow in onset, the maximum effect being achieved after only 1-2 months of treatment. They have similar glucose lowering effect with SU with a reduction in HbA1c by around 0.5–1.5% [58]. Estimates of insulin sensitivity and β-cell function have indicated that both defects can be improved by the addition of TZDs [13,58]. TZDs reduce hepatic glucose output and increase glucose uptake into muscle, enhancing the effectiveness of endogenous insulin and reducing the amount of exogenous insulin needed to maintain a given level of blood glucose by approximately 30%. Pioglitazone has also been found to reduce the risk of conversion from prediabetes to T2D by 72% [59].

The potential of these agents to reduce the risk of atherosclerotic CV disease have been reported [60]. With TZD treatment, the ratio LDL: HDL remains virtually unchanged. The proportion of small dense LDL particles (believed to be the most atherogenic) is reduced [58]. Pioglitazone treatment, in contrast to rosiglitazone, has shown significant protection from both micro- and macro-vascular CV events and plaque progression [61]. There is some evidence for a modest blood pressure-lowering effect of the TZDs [62].

5.4 Adverse Effect and Other Limitations [1]

5.4.1 Hepatitis

The withdrawal of troglitazone has led to concerns of the other TZDs also increasing the incidence of hepatitis and potential liver failure (an approximately 1 in 20,000 individual occurrence with troglitazone).

5.4.2 Cardiovascular risk

Rosigliazone and pioglitazone have been implicated with CV risk and they have been banned in many countries.

5.4.3 Bladder cancer

Preliminary data from a 10-year epidemiological study indicated a possible link between pioglitazone and bladder cancer. The findings prompted the FDA to order safety reviews for the drug in September 2010 [63,64] while some countries have suspended the drug.

5.4.4 Water retention and weight gain

Weight gain of 1-4 kg is common, usually stabilizing in 6-12 months. Some of this is attributable to fluid retention and this may lead to heamoglobin reduction. Fluid retention may precipitate congestive heart failure while reduction in haemoglobin concentration may lead to anemia.

5.4.5 Other adverse effects

Other adverse effects reported with these agents include:

- Symptoms of uncertain cause, including headache, fatigue and gastrointestinal disturbances;
- They are associated with increased risk of limb fractures;
- They are expensive;
- They are of slower onset of action compared to others.

6. ALPHA-GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibitors are oral anti-diabetic drugs used for T2D that work by preventing or delaying the digestion of carbohydrates to simple sugars in the intestine. The drugs in this class

include: acarbose, miglitol and voglibose. The prototype of this group (acarbose) was the first to be introduced in 1990s. They are saccharides in nature, acarbose is a pseudo-oligosaccharide isolated from the culture broths of various actinomycetes, whereas miglitol and voglibose resemble a monosaccharide. The chemical structures of acarbose and miglitol are shown in Fig. 5.

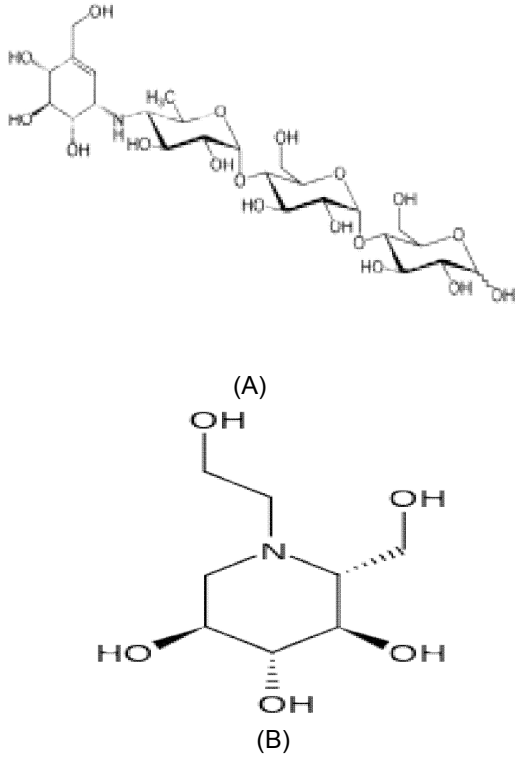


Fig. 5. Molecular structure of acarbose (A) and miglitol (B)

6.1 Mode of Action

Alpha-glucosidases are saccharides that act as competitive inhibitors of alpha-glucosidase enzymes in the brush border of the small intestines [1]. The membrane-bound intestinal alpha-glucosidases hydrolyse oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Acarbose also blocks pancreatic alpha-amylase in addition to inhibiting membrane-bound alpha-glucosidases. Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine. Miglitol also inhibits pancreatic alpha-amylase enzyme but only at very high concentrations. Voglibose is a very potent inhibitor of maltase and sucrose activity (K values of 3.8 and 2.0 nM, respectively), but also has little effect on pancreatic α-amylase [1]. Lactase is inhibited only at very high concentrations by miglitol, and not inhibited by acarbose. For *in vitro* assessment of α-glucosidase activity, inhibition of the hydrolytic activities of intestinal brush border membrane preparations or pancreatic homogenates toward various substrates (maltose, isomaltose, sucrose, etc.) are used in quantitative assays [1].

The inhibition of the enzymes delays the completion of carbohydrate digestion until further along the intestinal tract which then causes glucose absorption to be delayed [13]. This delayed glucose absorption reduces the postprandial rise in glucose level in diabetic patients. The delay also causes glucose-dependent release of intestinal hormones. These hormones (incretins), gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (7–36 amide), have insulinotropic effect that lower the blood sugar [13,26]. Thus the antidiabetic activity of α-glucosidase inhibitors may be partly mediated by alterations in the release of incretins as described above.

6.2 Pharmacokinetics

Acarbose has a low absorption of about 2% of orally administered drug. Unlike acarbose, miglitol is systemically absorbed in a dose dependent manner. Low doses (25 mg) of miglitol are completely absorbed, but absorption is saturable; it is incomplete at higher doses with peak plasma concentrations occurring in 2-3 h. Voglibose is very poorly absorbed. The volume of distribution of acarbose, 0.18 L/kg, is consistent with distribution primarily into extracellular water and binding to plasma proteins is negligible. Protein binding of miglitol is negligible (<4%). Acarbose is extensively degraded in the intestinal tract by digestive enzymes or intestinal microorganisms and eliminated in feces and urine. Miglitol is renally (95%) excreted as unchanged drug, with a plasma elimination half life of 2 h. Voglibose is excreted mainly through the feces as unchanged drug [1].

6.3 Indications and Efficacy

Postprandial hyperglycemia is primarily due to first phase insulin secretion. Alpha glucosidase inhibitors delay glucose absorption at the intestine level and thereby prevent sudden surge

of glucose after a meal. Thus they are used in the treatment of T2D to reduce the rate of appearance of glucose in circulation after a carbohydrate-containing meal and hence to reduce postprandial hyperglycemia. There are several trials supporting the use of these drugs in the management of postprandial hyperglycemia. It has been established that it is postprandial hyperglycemia, not fasting blood glucose, which is the marker of CV disorders associated with diabetes. They delay the absorption of glucose thereby reducing the risk of macrovascular complications. In diabetic patients, the short-term effect of these drugs therapies is to decrease current blood glucose levels while the long-term effect is a reduction in HbA1c level [65]. Acarbose reduces FBG by 1.4-1.7 mmol/L, postprandial glucose levels by 2.2-2.8 mmol/L, and HbA1c values by 0.7-1% [21]. Miglitol appears to be rather similar and voglibose is particularly indicated for the management of postprandial hyperglycemia. Thus these agents, although less efficacious than the SU or metformin, reduce fasting as well as postprandial hyperglycemia. They must be taken at the start of main meals to have maximal effect and their effect will depend on the amount of non-monosaccharide carbohydrates in a person's diet. Thus it is important to ensure that the patient is taking a diet rich in complex carbohydrates as opposed to simple sugars [13].

They are also effective in preventing the progression of prediabetes to diabetes. For instance, a recent multicentre clinical trial (STOP-NIDDM, Study TO Prevent Non-Insulin Dependent Diabetes Mellitus) confirmed the utility of acarbose in preventing the transition from impaired glucose to diabetes. New cases of hypertension and major cardiac events including overt and clinically silent myocardial infarction were also reduced by acarbose therapy [66]. Recent study on rats showed that miglitol has antioxidant effect and hypocholesterolemic effect [67].

Unlike SU, miglitol and acarbose do not cause hypoglycemia, hyperinsulinemia or weight gain. They do have the potential to cause weight loss by lowering the amount of sugar metabolized. Voglibose scores over both acarbose and miglitol in terms of side effect profile but acarbose has an edge over voglibose in terms of efficacy [1].

6.4 Adverse Effect and Other Limitations

6.4.1 Gastrointestinal effects

Gastrointestinal disturbances in the form of flatulence, abdominal discomfort, and, to a lesser extent, diarrhea, are common side effects of therapy with alpha-glucosidase inhibitors. In the STOP-NIDDM trial, 31% of acarbose-treated patients compared with 19% on placebo discontinued the treatment early [66]. If the dosage is too high (relative to the amount of complex carbohydrate in the meal), undigested oligosaccharides pass into the large bowel causing the above gastrointestinal effects when fermented by the flora of the large bowel [18].

6.4.2 Elevated serum transaminase

Higher doses of acarbose (100 mg or greater) has been associated with a low incidence of elevated serum transaminase levels, most often in patients weighing less than 60 kg [1].

6.4.3 Hepatitis

Hepatitis has been reported with acarbose use. It usually goes away when the medicine is stopped [68]. Therefore, liver enzymes should be checked before and during the use of this medicine.

6.4.4 Other limitations

- They are less effective than most other diabetes pills in reducing HbA1c;
- They are expensive.

7. SODIUM GLUCOSE OTRANSPORTERS 2 (SGLT2) INHIBITORS

These are drugs that lower the blood glucose by inhibiting the sodium glucose co-transporters 2 (SGLT 2). A natural compound isolated from the bark of apple trees, phlorizin, was the first SGLT inhibitor discovered in 1835 but not suitable for clinical use because of poor bioavailability and adverse effects such as diarrhea [69,70]. Recently, several drug candidates have been developed or are currently undergoing clinical trials. These include: dapagliflozin, approval rejected by FDA due to safety concerns [71] but marketed in Europe), canagliflozin (approved in the United States) [72], ipragliflozin (in Phase III clinical trials), tofogliflozin (in Phase III clinical trials), empagliflozin (in Phase III clinical trials) [73], sergliflozin etabonate (discontinued after

Phase II trials) and remogliflozin etabonate (in phase IIb trials).

Only dapagliflozin and canagliflozin are currently approved for use in diabetes. In July 2011 an FDA committee recommended against approval of dapagliflozin until more data was available [71]. On the contrary, in April 2012, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency issued a positive opinion on the drug. It is now marketed in a number of European countries including the UK and Germany. In March 2013, canagliflozin (Invokana®) became the first SGLT2 inhibitor to be approved in the United States [72] but was approved in Europe in November 2012. Their chemical structures are shown in Fig. 6.

7.1 Mode of Action

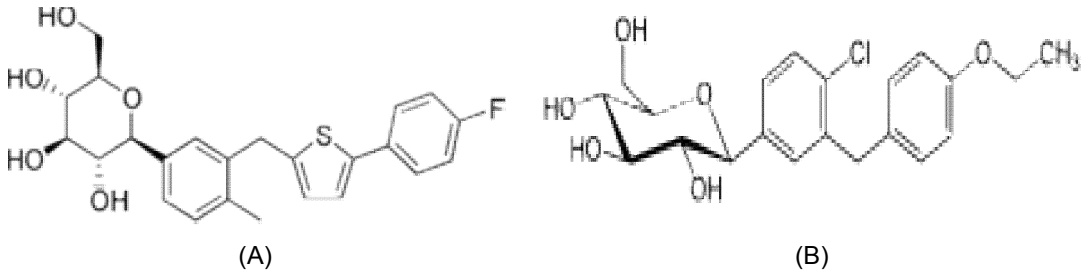
SGLT1 and SGLT2 are proteins that, in humans, are encoded by the SLC5A2 (solute carrier family 5 (sodium/glucose cotransporter) gene [74]. The proteins (SGLT1 and SGLT2) are glucose transporters found in the intestinal mucosa (enterocytes) of the small intestine (SGLT1) and the proximal convoluted tubule (PCT) of the nephron (SGLT2 in early PCT and SGLT1 in later part of PCT) [3, 69, 70]. They contribute to renal glucose reabsorption. In the kidneys, 100% of the filtered glucose in the glomerulus has to be reabsorbed along the nephron (98% in PCT, via SGLT2). In case of too high plasma glucose concentration (hyperglycemia), SGLT becomes saturated with the filtered monosaccharide and glucose is excreted in urine (glucosuria) [75]. This capacity for glucose reabsorption increases in diabetics due to the upregulation of SGLT2 and GLUT2 in the proximal tubule, resulting in hyperglycemia and reduced glucosuria [3,4]. SGLT 2 inhibitors inhibit SGLT2, which is responsible for about 98% of the glucose re-absorption in the kidney. Blocking this transporter causes blood glucose to be eliminated through the urine [76]. These drugs do not interfere with the intestinal glucose absorption because the SGLT2 are more receptive than the SGLT1 located predominantly in the intestine [77].

7.2 Pharmacokinetics

They are orally administered. Bioavailability after oral administration of canagliflozin is 65% and dapagliflozin is rapidly absorbed with bioavailability of 78%. Generally dapagliflozin achieve peak plasma concentrations within 2 h [78]. Canagliflozin is highly protein bound (99%). Canagliflozin is metabolized by hepatic glucuronidation with half life of 10-13 hours. Excretion is by fecal and renal routes. Dapagliflozin is also mainly metabolized by glucuronidation to dapagliglozin-3-O-glucuronide (not an SGLT2 inhibitor) which is eliminated primarily through the renal route with half life of 12.9 h [78].

7.3 Indications and Efficacy

They are indicated as monotherapy or as add-on therapy in T2D. On November 12, 2012 the European Commission approved use of dapagliflozin 10 mg once daily in T2D to improve glycemic control as monotherapy when diet and exercise alone do not provide adequate glycemic control in patients for whom the use of metformin is considered inappropriate due to intolerance. It was also approved in Europe as add-on therapy with metformin, SU, or with insulin (±OHA), together with diet and exercise, when these agents do not provide adequate glycemic control [3]. Although the mode of action of agents in this class would operate on both types of diabetes and other conditions resulting in hyperglycemia, the clinical trials specifically excluded participants with T1D [79].



(A) (B)

Fig. 6. Chemical structure of canagliflozin (A) and dapagliflozin (B)

The long term post-marketing efficacy of this medication class has yet to be determined, but in phase III clinical trials, these agents are effective either alone or in combination with other agents. Dapagliflozin 5 mg and 10 mg maintains a reduction in HbA1c of 0.71% and 0.61% respectively versus placebo (0.17%) after 102 weeks of therapy in T2D patients [80]. This long-term study discovered the initial blood pressure reductions seen at 24 weeks gradually returned to baseline by week 102; however, this study did not control for changes in background antihypertensive medications, a large limitation to the study results [80]. When added to metformin, dapagliflozin lowers HbA1c by 0.90% [81,82]. CANVAS (CANagliflozin cardioVascular Assessment Study, a double-blind placebo-controlled phase III clinical trial) report showed that canagliflozin decreased weight by a 1.9 - 3% as well as decreased HbA1c by 0.57-0.70%, reduced both systolic and diastolic blood pressures [83] and raised HDL cholesterol [84]. Other potential benefits of this class of medication, as seen from clinical trials, include reduction of uric acid (ranging from −5.9% to −17.8%) and lipids profile [3].

7.4 Adverse Effect and Other Limitations

7.4.1 Infections

Since the drugs lead to heavy glycosuria (sometimes up to about 70 g/day) as part of their action, this can lead to polyurea, rapid weight loss, dehydration and tiredness; glucose acts as an osmotic diuretic leading to dehydration. The increased amount of glucose in the urine can also worsen the infections already associated with diabetes, particularly urinary tract infections and thrush (candidiasis).

7.4.2 Cardiovascular concern

The CANVAS trial showed some concern about CV events with canaglifloxin. Although final results from the CANVAS trial are not expected until 2015, during the first 30 days after randomization in CANVAS, there were 13 CV events in the patients receiving canagliflozin (0.45%) versus 1 in patients receiving placebo (0.07%). The hazard ratio of 6.5 was not significant because of the small number of events [85]. Also, on approval, the FDA is requiring five post-marketing studies for canagliflozin, including a CV outcomes trial, an enhanced pharmacovigilance program (to monitor for malignancies, serious cases of pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes), a bone safety study, and two pediatric studies [86].

- Other adverse reports/limitations include the following: There were reports of canagliflozin increasing LDL cholesterol, urinary tract infections, genital mycotic infections, and was associated with increased urination and episodes of hypotension and hypoglycemia [83]. There has been concern about the risk of bone fracture with canagliflozin [87] but this has not been proved by Dual-energy X-ray absorptiometry (DEXA) results [3].
- Dapagliflozin is also associated with hypotensive reactions. When comparing the results of various clinical trials, dapagliflozin appears to have a higher frequency of adverse effects than canagliflozin. The drugs are contraindicated in patients with renal impairment. In a study in patients with moderate renal impairment, dapagliflozin use does not significantly improve HbA1c or FBG [88].

8. DPP-4 INHIBITORS

These are the inhibitors of dipeptidyl peptidase-4 enzyme, also DPP-4 inhibitors or gliptins. The first agent, sitagliptin [89] was approved by FDA in 2006. Others include: vildagliptin [90] (EU approved in 2008), saxagliptin (FDA approved in 2009), linagliptin (FDA approved in 2011) [91], anagliptin (approved in Japan in September 2012) [92] and alogliptin (FDA approved in 2013). The chemical structures of some of these are shown in Fig. 7.

8.1 Mode of Action

They act by competitively inhibiting the enzyme DPP-4. The enzyme is a serine protease which is widely distributed in human tissues, including the pancreas, lungs, intestines, kidneys, brain, adrenals and lymphocytes [93]. It breaks down the incretins, GLP-1 and GIP, which are gastrointestinal hormones released in response to a meal [94]. These hormones have insulinotropic effect. By preventing GLP-1 and GIP inactivation, they tend to increase and prolong the incretins, especially the GLP-1, in T2D patients [95]. This increases the secretion of insulin and suppresses the release of glucagon by the pancreas, thereby reducing blood glucose levels in the diabetic patients.

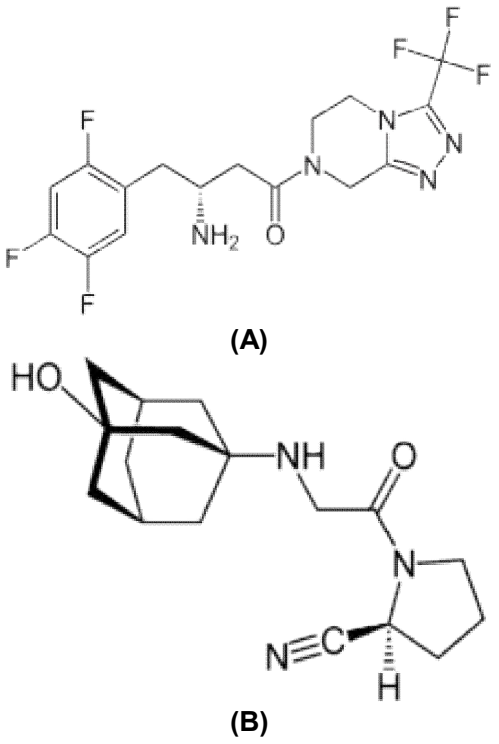


Fig. 7. Chemical structures of sitagliptin (A) and vildagliptin (B)

8.2 Pharmacokinetics

Absorption and distribution: Sitagliptin has oral bioavailability of about 87% and protein binding of 38%. Vildagliptin is 85% absorbed after oral administration and protein binding is low (9.3%). The bioavailability of linagliptin in humans is only about 30% with almost complete plasma protein binding [96].

Metabolism and elimination: Vildagliptin is primarily metabolized by hydrolysis (P450 not involved) to inactive metabolite with half life of 2 to 3 hours and excreted in the urine. Linagliptin is not metabolized by CYP 450 and does not interfere with drugs metabolized by this enzyme [96]. Linagliptin is mostly eliminated by a biliary/hepatic route with very low renal route (about 1%–6%). This property allows the use of linagliptin in T2D patients with normal renal function and also in patients with renal insufficiency without dose adjustments [97].

8.3 Indications and Efficacy

These agents are used in T2D patients either in monotherapy or in combination with other antidiabetic agents. They are generally recommended as a second line drug (in combination with other drugs) after the combination of diet/exercise and metformin fails. Since they are newly introduced, long time post-marketing efficacy data are lacking but data from clinical trials have been encouraging. Sitagliptin was shown to lower HbA1c by about 0.7% compared to placebo [98]. Though slightly less effective than metformin when used as a monotherapy, sitagliptin does not cause weight gain and it produces less hypoglycemia than SU. Vildagliptin has equally been shown to reduce hyperglycemia in T2D patients [99].

Oral saxagliptin 2.5 or 5 mg once daily suppresses DPP-4 activity for 24 hours [100]. Mean HbA1c levels are also significantly improved (relative to placebo) in a 24-week trial in T2D patients [101]. The placebo-adjusted HbA1c reduction with saxagliptin (2.5 to 40 mg) ranged from 0.45% to 0.63% [102]. In a trial study, combination therapy with saxagliptin 5 mg once daily and metformin was more effective than saxagliptin or metformin monotherapy. Clinically relevant reductions in HbA1c were obtained with saxagliptin when used as add-on to patients on metformin in randomized, double blind, placebo-controlled, multicenter study that enrolled 743 patients with T2D. In the study, β-cell function measured by the HOMA-2β (homeostasis model assessment) method was found to be improved in all saxagliptin-treated groups [103]. In terms of CV risk, a meta-analysis did not show evidence of increased CV risk in T2D patients treated with saxagliptin for up to 2.5 years [104]. Saxagliptin was found to have weight neutral effects when used as monotherapy [105] or in combination with metformin [105,106].

In phase III clinical trials in Japanese patients, linagliptin exhibits a placebo-subtracted HbA1c reductions of 0.27%, 0.27%, and 0.42% for the doses of 2.5 mg, 5 mg, and 10 mg respectively after 4 weeks of treatment [106,107]. Placebo-subtracted reduction in HbA1c of 1.3% and 1.7%, respectively have been reported in combination therapy of metformin and linagliptin. In a sub-group receiving the combination therapy, HbA1c reduction of 3.7% was also reported [108]. The beneficial effect of linagliptin in T2D patients with severe renal impairment have also been reported [109,110]. Linagliptin is primarily eliminated by hepatobiliary route, thus it is approved for use in patients with declining renal function without dose adjustment [111].

In the HOMA-B method of assessment, there was improvement in plasma insulin which worsened with placebo in T2D patients exposed to alogliptin. Alogliptin treatment reduced the FBG and HbA1c levels in the patients [112]. Also preclinical data from obese diabetic ob/ob mice shows 1.5–2.0 fold increase in plasma insulin after 4 weeks of treatment with alogliptin [113]. More recently, improved human insulin secretion and β-cell proliferation by alogliptin was demonstrated in human islet-engrafted immune-deficient mice [114].

8.4. Adverse effects and other limitations

8.4.1 Pancreatitis

There have been several post-marketing reports of pancreatitis which are fatal in some cases in people treated with sitagliptin and other DPP-4 inhibitors [115]. The U.S. package insert carries a warning to this effect [116] and this is under investigation by the FDA and the European Medicines Agency (EMA) [117].

8.4.2 Cancer

It is thought that inhibiting the DPP-4 enzymes may allow some cancers to progress since these enzymes are known to be involved in suppression of some types of malignancies [118,119]. A study of DPP-4 enzyme inhibition in human non-small cell lung cancer (NSCLC) concluded that inhibition of the enzymes may contribute to the loss of growth control in NSCLC cells [120]. This area is unclear at the moment and needs further investigations.

8.4.3 Hepatitis

There have been reports of rare cases of acute hepatitis and skin ulceration in experimental animals with vildagliptin. Though the drug is approved by EMA in 2008, it has not received FDA approval. The drug is listed on the Australian PBS but with certain restrictions [121].

8.4.4 Other adverse effects

Other adverse effects reported include rare cases of nausea and common cold-like symptoms, including photosensitivity which was noted during clinical trial of sitagliptin. Spontaneously-reported adverse events of saxagliptin include anaphylaxis, angioedema. In clinical trials, the most frequently reported adverse events with linagliptin (linagliptin vs placebo) were headache (21% vs 38%), influenza-like illness (11% vs 4%), and nausea (4% vs 6%) [122]. The outcome of the ongoing CV study on linagliptin (CAROLINA) will provide a value data for the CV effect of linagliptin in comparison to glimepiride [122,123].

9. DUAL PPAR AGONISTS

PPAR agonists are drugs which act upon the peroxisome proliferator-activated receptor (PPAR). They are used for the treatment of symptoms of the metabolic syndrome, mainly for lowering TG and blood sugar. The main classes of PPAR agonists are: PPARα, PPARγ, PPARδ and the dual PPAR or pan PPAR agonists. PPARα is indicated for cholesterol disorders and disorders that feature high TG. It is the main target of fibrate drugs such as clofibrate. PPARγ is the main target of the TZDs (discussed above). It has been shown that agonism of PPARδ changes the body's fuel preference from glucose to lipids [124], but ironically improves metabolic syndrome (which is characterized by the body being unable to efficiently deal with glucose resulting in insulin resistance and sometimes diabetes) [125].

A fourth class of dual PPAR agonists, so-called glitazars, which bind to both the α and γ PPAR, are currently under active investigation for treatment of metabolic syndromes [126]. These include the experimental compounds aleglitazar, muraglitazar and tesaglitazar. In June 2013, saroglitazar Fig. 8 became the first glitazar to be approved for clinical use. Saroglitazar (Lipaglyn™) was developed and marketed by Zydus Cadila, Ahmedabad, India. It is approved for use in India by the Drug Controller General of India. It is the first indigenously developed NCE by any Indian pharmaceutical company, ever [127]. It is available as an oral tablet containing 4 mg of saroglitazar. New dual α/δ and γ/δ PPAR agonists as well as pan agonists acting on all three isoforms are also under investigation [128,129].

9.1 Mode of Action

Saroglitazar is a potent and predominantly PPAR-alpha agonist with moderate PPAR-gamma agonistic activity. PPARs are nuclear lipid-activated transcription factors that regulate the expression of various genes involved in the control of lipid and lipoprotein metabolism,

glucose homeostasis and inflammatory processes. Saroglitazar shows both anti-dyslipidemic and anti-diabetic effects mainly mediated via activation of PPARα and PPARγ respectively. PPARα activation by saroglitazar increases the hepatic oxidation of fatty acids (FA) and reduces the synthesis and secretion of TG. This in turn increases diversion of FA from peripheral tissues (e.g. skeletal muscle and fat tissue) to the liver, and thereby decreasing both FA synthesis and delivery of TG to peripheral tissues. It also causes activation of PPARγ and regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization [130].

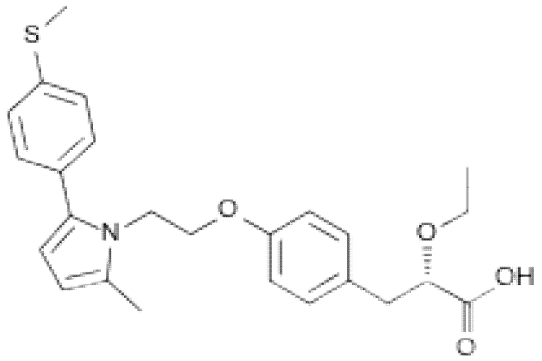


Fig. 8. Chemical structure of sitaglitazar

9.2 Pharmacokinetics

Following oral administration in healthy volunteers, peak plasma levels of saroglitazar occurred at approximately 1 hour post-dosing. Protein binding is approximately 96% in human plasma. Saroglitazar is metabolized into three minor oxidative metabolites. It is eliminated through non-renal route of elimination, predominantly unchanged by the hepatobiliary route [94].

9.3 Indications and Efficacy

Saroglitazar is a drug for the treatment of diabetic dyslipidemia and hyper-triglyceridemia with T2D patients not controlled by statin therapy. Being recently introduced, post marketing efficacy data are lacking but results of clinical trials are encouraging. The first Phase III clinical trials on saroglitazar showed that patients who were administered with 4 mg dose exhibit reduction in LDL cholesterol and TG, and increase in HDL cholesterol. The study also showed that saroglitazar-administered patients have a reduction in FBG and HbA1c. The second Phase III clinical trials on saroglitazar were conducted to evaluate the diabetic dyslipidemic patients insufficiently controlled with statin therapy. Results showed that patients treated with saroglitazar show pronounced beneficial effect on both the lipid and glycemic parameters [131].

There was no incidence of hypoglycemia reported during Phase I-III trials in both diabetic and non-diabetic subjects. The effects of saroglitazar at a dose of 4 mg per day were assessed in two Phase-III randomized, double-blind, parallel-group studies including diabetic patients with TG >200 mg/dL. In one study, the patients were treated with saroglitazar 4 mg or pioglitazone (45 mg) for 24 weeks. Saroglitazar achieved the ATP III (Adult Treatment Panel III of US National Cholesterol Educational Program, 2002-2003) goal in more subjects than pioglitazone. In another study, the effect of saroglitazar at 4 mg per day was assessed in diabetic patients with hypertriglyceridemia not controlled with atorvastatin 10 mg therapy. The patients were treated with saroglitazar 4 mg or placebo for 12 weeks along with atorvastatin 10 mg. In combination with atorvastatin saroglitazar achieved the ATP-III goal in more subjects than atorvastatin alone; hence demonstrating better CV risk reduction [130].

In non clinical acute toxicity studies, the maximum tolerated dose (MTD) in Swiss albino mice was 500 mg/kg, and in Wistar rat it was 1200 mg/kg. Safety pharmacology studies did not reveal any adverse changes in central nervous system, CV, respiratory and gastrointestinal parameters. In repeat dose toxicity studies, saroglitazar was shown to have an acceptable safety profile at doses several fold higher than the approved human doses [130].

9.4 Adverse Effect and Other Limitations

The most common adverse events (AEs ≥ 2%) reported with saroglitazar were gastritis, asthenia and pyrexia. The product (Lipaglyn™) insert [130] has the warnings stating the following:

- Although clinical studies have not demonstrated any potential for myopathies or derangement of liver and/or renal function, saroglitazar treatment should be initiated with caution in patients with

abnormal liver or renal function, or history of myopathies.

- Saroglitazar has not been studied in patients with established New York Heart Association (NYHA) Class III or IV heart failure; hence the drug should be initiated with caution in patients with type 2 diabetes having cardiac disease with episodic congestive heart failure and such patients should be monitored for signs and symptoms of congestive heart failure.
- Although during the clinical studies, no significant weight gain and edema was reported with saroglitazar, patients who experience rapid increase in weight should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

10. DISCUSSION AND CONCLUSION

The effects, efficacy and safety profile of the various OHA presented in this review are summarized in Table 1. The glucose-lowering effect of the major classes of OHA is broadly similar with average of 1–2% reduction in HbA1c. Among the five existing classes of agents (SU, meglitinides, biguanides, TZDs and the alpha-glucosidase inhibitors, the latter is less effective. It is reported that maximal glucose-lowering action for SU is usually attained at appreciably lower doses (approximately 50%) than the manufacturers' recommended daily maximum [13].

Though slightly less efficacious than the existing agents, the SGLT-2 inhibitors improve glucose control to an extent comparable to other hypoglycemic agents while simultaneously reducing body weight, blood pressure, and cholesterol [3]. Risk of cancer and the fact that they are new agents warrants careful monitoring when used in patients. DPP-4 inhibitors appear to effect high HbA1c reduction which is comparable to that of metformin. They also offer an attractive safety and tolerability profile, with a low risk of hypoglycemia and gastrointestinal intolerance when added on to existing therapy, compared with a glinide or SU [95,132,133]. The apparent superiority of DPP-4 inhibitors is also reflected in the number of drugs (six) approved in this class since the approval of the first drug, sitagliptin, in 2006. The importance of DPP-4 inhibitors in T2D has been recognized by their inclusion in the treatment algorithm of T2D patients which is reflected in the recent position statement by ADA and the EASD (European Association for the Study of Diabetes) [134]. The fixed dose combinations of some of the DPP-4 inhibitors with metformin are already in the market [97]. Specifically, linagliptin, a DPP-4 inhibitor may be favorable for older patients with declining renal function because of pharmacokinetic profile [122]. The dual PPAR agent, saroglitazar finds a place in the treatment of T2D patients with dyslipidemia and hyper-triglyceridemia.

Upon diagnosis of T2D, the patients are advised on the central importance of lifestyle interventions such as following an appropriate diet, and the performance of regular physical exercise. It is required that this is adhered to throughout the course of the disease, regardless of the therapy type used [12]. OHAs are used as monotherapy or combination therapy depending on the ß-cell function reserve and level of insulin resistance [12]. Choice of an OHA depends on the likely predominating pathogenetic mechanism. It is rational to start a recently or newly diagnosed T2D patient, especially if symptomatic, on a single class of OHA, ie, monotherapy [135]. Metformin is considered as the initial medication in all T2D, but not when body mass index (BMI) is below 25 and ketones are present [135]. A common combination treatment is with an SU and metformin. Clinical experience suggests this controls most new patients, where diet alone is insufficient, and should be considered when BMI is 20-25 [135]. When considering long-term therapy, issues such as tolerability and convenience are important additional considerations.

In conclusion, the introduction of newer OHA agents in the treatment of T2D increases the treatment or drug options for a clinician. Careful assessment of the patient and rational choice of the OHA either as an initial monotherapy or in polypharmacy is required. Metformin is still considered a first choice oral agent in T2D but newer agents should be used with caution and constant monitoring of the patients. The efficacy and safety information provided in this review could be of help in the choice of the agent for the T2D patients.

Table 1. Summary of the actions, efficacy and safety of the various oral anti diabetic agents

S/N	Drug class	Drugs	Mode of Action	Efficacy (HbA1c reduction)	Major adverse effect
1	Sulphonyl-ureas	acetohexamide, chlorpropamide, tolbutamide, tolazamide, glipizide, gliclazide, glibenclamide glibornuride, glimepiride	Insulin secretagogue/ releaser	1-2%	Hypoglycemia, weight gain
2	Meglitinides	repaglinide, nateglinide	Insulin secretagogue/re leaser	1.5-2%	Hypoglycemia
3	Biguanides	metformin	Insulin sensitizer	1-2%	GIT effects, Lactic acidosis (rare)
4	Thiazolidine-diones	rosiglitazone, pioglitazone	Insulin sensitizer	0.5-1.5%	Hepatitis, CV risk, bladder cancer, weight gain
5	Alpha-glucosidase inhibitors	acarbose, miglitol and voglibose	Reduces post prandial rise in glucose level in diabetics	0.7-1%	GIT effects
6	Sodium glucose cotranspor-ters 2 (SGLT2) inhibitors	dapagliflozin, canagliflozin	Blocks the reabsorption of glucose from the kidney	0.5-0.7%	Rapid weight loss, dehydration, infections, risk of cancer
7	DPP-4 Inhibitors	sitagliptin, vildagliptin, saxagliptin, linagliptin, anagliptin, alogliptin	Inhibit the enzymes that break down the incretins	0.27-1.7%	Pancreatitis, cancer, acute hepatitis, cancer,
8	Dual PPAR agonists	saroglitazar	anti-dyslipidemic and insulin sensitizer	Reductions in LDL, TG and HbA1c	gastritis, asthenia and pyrexia

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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