Review Article

Role of conventional oral antidiabetic drugs in management of type 2 diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is caused by insulin resistance and characterized by progressive pancreatic β-cell dysfunction. Recent innovative treatment approaches target the multiple pathophysiological defects present in type 2 diabetes. The targets for glycemic control as set by the American Diabetes Association (HbA₁C<7%) and the American Association of Clinical Endocrinologists (HbA1C<6.5%) sometimes appear daunting and unattainable. It is therefore of the utmost importance to have an excellent understanding of the mechanism of action of these drugs in order to optimize patient therapy. Here, we present a corresponding discussion of all the available oral antidiabetic drugs according to the different classes, their mechanisms of action and pharmacological profiles.

Keywords: India, Oral antidiabetic drugs, T2DM

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is caused by insulin resistance and characterized by progressive pancreatic β-cell dysfunction. If untreated or not managed well, long-term hyperglycaemia can lead to increased risk of macrovascular (cardiovascular, cerebrovascular and peripheral vascular disease) and microvascular (nephropathy, neuropathy and retinopathy) complications. Diabetes may affect nearly 10% of individuals in the United States and its economic toll as well as its costs in terms of morbidity and mortality are staggering.¹ Prescription medications for diabetes and testing supplies account for 12% of the medical expenditures for diabetes but they are often ineffective in getting patients to goal.² Study based on data from the national health and nutrition examination survey found that about 45% of patients with diabetes lacked adequate glycaemic control.³ The targets for glycaemic control as set by the American diabetes association (HbA₁C<7%) and the American association of clinical endocrinologists (HbA₁C <6.5%) sometimes appear daunting and unattainable.⁴,⁵ Current outpatient regimens are also limited by issues of safety and tolerability. Severe hypoglycemia is one of the most important side effects of treatment for diabetes, and it occurs at a rate of over 10 events per 100 patient-years in patients with type 2 diabetes who start basal insulin.⁶ Having a hypoglycemic event was associated with a higher rate of treatment discontinuation for anti-diabetes drugs. Poor adherence to prescribed anti-diabetes treatment, in turn, is independently associated with a higher risk for mortality. Although lifestyle modifications and metformin are the cornerstones of the initial management of T2DM, there is
an increasing array of second- and third-line pharmacological agents, including sulphonylureas, insulin, thiazolidinediones and glitazones, α-glucosidase inhibitors, glucagon-like peptide-1 agonists, dipeptidyl peptidase 4 inhibitors and the amylin receptor agonist pramlintide. Current outpatient regimens are also limited by issues of safety and tolerability. Many new drug classes currently in development for type 2 diabetes appear promising in early stages of development, and some of them represent novel approaches to treatment, with new mechanisms of action and a low potential for hypoglycemia. Among these promising pharmacotherapies are agents that target the kidney, liver, and pancreas as a significant focus of treatment in type 2 diabetes. The effectiveness of T2DM treatment therapy is often determined by indicators such as HbA\textsubscript{1C} levels. The American diabetes association recommends an HbA\textsubscript{1C} target of ≤7% in diabetic patients. Type 2 DM is often treated with insulin sensitisers (e.g. thiazolidinediones; TZDs), insulin secretagogues [e.g. sulphonylureas (SUs) and meglitinides] and external insulin delivery (insulin analogues). But the currently approved drugs decrease HbA\textsubscript{1C} level by only about 1-2%, and further, some have various side effects that include gastrointestinal intolerability, hypoglycaemia and weight gain among others.\textsuperscript{3}

**TYPES OF DIABETES MELLITUS**

**Type 1 DM- Insulin dependent diabetes**

Linked with the formation of antibodies, including insulin and the islet cells of the pancreas.\textsuperscript{10-14} It results from the destruction of insulin-producing b-cells. Initially, patients with type 1 DM display postprandial hyperglycaemia only, but these progresses to include fasting hyperglycaemia by the time β-cell destruction are complete. Type1 DM accounts for about 5-10% of the diabetic population. Because it is mainly an autoimmune disorder resulting in progressive destruction of pancreatic b-cells, patients usually have little insulin reserve at the time of diagnosis and therefore require some form of insulin pharmacotherapy for life.\textsuperscript{5-12}

**Type 2 DM- Non-insulin dependent diabetes**

Accounts for almost 90% of the diabetic population. Type 2 DM is characterized by dysfunction of pancreatic islet cells and insulin resistance and, secondarily, by an increased glucose production resulting from feedback control mechanisms. In an effort to overcome insulin resistance at tissue targets, additional insulin is produced in an effort to counteract the hyperglycaemia. This additional insulin contributes to hyperinsulinemia and down-regulation (decreased number) of insulin receptors located on target tissues. Although the exact mechanism of insulin resistance is not known, it is believed to be related to decreased insulin receptor binding affinity or to defects in insulin receptor signal transduction mechanisms. Genetics, obesity and sedentary lifestyle also play a role in diabetes.\textsuperscript{13,14}

**2015 AMERICAN DIABETES ASSOCIATION (ADA) DIABETES GUIDELINES**

**Diabetes diagnosis**

Criteria for diabetes diagnosis: 4 options

- HbA\textsubscript{1C} ≥6.5%
- FPG ≥126 mg/dL (Fasting defined as no caloric intake for ≥8 hrs)
- 2-hr PG ≥200 mg/dL (during OGTT (75-g))
- Random PG ≥200 mg/dL

**Testing for Type 2 Diabetes and prediabetes in asymptomatic adults**

Type 2 diabetes testing should be done in all adults who are overweight or obese (BMI ≥25 or ≥23 in Asian Americans) who have ≥1 diabetes risk factor.

**Diabetes risk factors**

- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity
- Women who delivered a baby >9 lb or were diagnosed with GDM
- HDL-C <35 mg/dL ± TG >250 mg/dL
- Hypertension (≥140/90 mm Hg or on therapy)
- HbA\textsubscript{1C} ≥5.7%, IGT, or IFG on previous testing
- Conditions associated with insulin resistance: severe obesity, acanthosis nigricans, PCOS
- CVD history

**Glycemic targets**

Glycemic targets for non-pregnant adults with diabetes

- HbA1C <7.0%
- Preprandial capillary PG 80-130 mg/dL
- Peak postprandial capillary PG <180 mg/dL

More or less stringent targets may be appropriate if can be achieved without significant hypoglycaemia or adverse events.

- More stringent target (<6.5%)
- Less stringent target (<8%)

**Pharmacologic Therapy for Type 2 Diabetes**

Metformin: Preferred initial therapy (if tolerated and not contraindicated) when lifestyle changes alone have not achieved or maintained glycemic goals.
Consider insulin therapy with or without other agents: At outset in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1C

Add 2nd oral agent, GLP-1 receptor agonist, or insulin: If non-insulin monotherapy at maximal tolerated dose does not achieve or maintain A1C target over 3 months.

Choice of pharmacologic therapy should be based on patient-centred approach, considering

- Efficacy
- Cost
- Potential side effects
- Effects on weight
- Comorbidities
- Hypoglycemia risk
- Patient preferences

Oral hypoglycemics available for treatments

- Biguanides
- Sulfonylureas
- Thiazolidinediones(Glitazones)
- α-glucosidase inhibitors
- Incretin mimetics
- Glucagon-like peptide (GLP) -1 agonists
- Dipeptidyl peptidase (DPP)-4 inhibitors

Amylin receptor agonist

SGLT-2 inhibitors

Meglitinide analogues

Bile acid sequestrants

Drugs in Pipeline

- Glucagon-Receptor Antagonists
- Protein Tyrosine Phosphatase 1B Inhibitors
- G Protein–Coupled Receptor 119 Agonists
- Glycogen Phosphorylase Inhibitors

INSULIN SENSITISERS

Biguanides

- Metformin
- Phenformin- withdrawn from the market due to the risk of lactic acidosis.
- Buformin- withdrawn from the market due to the risk of lactic acidosis.

Metformin has been available since the 1950s. It has variety of clinical actions that extend beyond just the glucose lowering effects such as weight reduction, improving lipid profiles and vascular effects, which includes improving endothelial function, as well as decreasing PAI-1 levels.15

Mechanism of action

Biguanides have a twofold mechanism of action.

- They enhance peripheral muscle glucose uptake and utilization by making muscle and fat cells more sensitive to available insulin
- They inhibit hepatic glucose output by preventing the liver from making excessive glucose.56

It is thought that insulin sensitivity is improved and mediated via modification of post-receptor signalling in the insulin pathway. The mainstay of action of this class of drug can be attributed to its hepatic effects. Hepatic sensitivity to insulin is increased, thereby reducing gluconeogenesis as well as glycogenolysis, which contributes to the post-prandial plasma glucose lowering effects. Skeletal muscle and adipocytes undergo up-regulation of the insulin-sensitive GLUT- 4 and GLUT-1 transporters to the cell membranes, thereby increasing glucose uptake. Glucose metabolism in the splanchnic bed also increases. Further metabolic effects include suppression of fatty acid oxidation as well as triglyceride lowering.17,18

Important pharmacokinetic properties

It is fully eliminated in the urine via tubular secretion. Therefore, it is prudent to avoid this drug in patients with impaired renal function. Metformin should be discontinued prior to contrast studies, e.g. angiographic evaluations, since it has been implicated in the development of contrast-induced nephropathy.

Current place in the therapy

Metformin is considered as the drugs of choice in obese type 2 diabetics. Metformin can be used in combination with any other class of oral antidiabetic drug or with insulin. When used at optimal dosages, the decrease in fasting glucose levels is estimated at 2 - 4 mmol/l, with a drop in HbA1C levels of 1 - 2%.19

Adverse effects

This includes

- Lactic acidosis: It increases lactate production in the splanchnic bed and portal venous system due to a reduction in the activity of pyrovate dehydrogenase enzyme, thereby shifting the metabolism towards the anaerobic spectrum. However, the incidence of metformin induced lactic acidosis is extremely rare, with only 0.03 cases per 1 000 patient-years reported in the literature.
Abdominal discomfort and diarrhoea are the most frequent side-effects. Vitamin B12 deficiency owing to decreased GIT absorption can occur.

**Advantages**
- Low risk of hypoglycemia, even in overdose.
- Weight neutral as monotherapy, and nullifies weight gain as a side effect of other antihyperglycemic agents, including insulin.

**Pre-diabetes**

The chance of developing type 2 diabetes mellitus may decrease in people at risk for this disease.20 Several trials have suggested that metformin is as safe and effective as insulin for the treatment of gestational diabetes.21

**Table 1: Combinations with metformin.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Manufacturing company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>Actoplus Met</td>
<td>Takeda Pharmaceuticals,</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Metaglip</td>
<td>Bristol-Myers</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>Glucovance</td>
<td></td>
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<tr>
<td>Glyburide</td>
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<td></td>
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<tr>
<td>Sitagliptin</td>
<td>Janumet</td>
<td>Merck</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Kombiglyse XR</td>
<td>AstraZeneca</td>
</tr>
</tbody>
</table>

**Sulfonylureas**

The oldest noninsulin drug class presently available for the treatment of T2DM, have been the main pharmacologic approach for treatment of T2DM for many decades because of their reliable efficacy in newly diagnosed patients, limited side effects (mainly hypoglycemia) and low cost.

**First generation**
- Tolbutamide
- Chlorpropamide

**Second generation**
- Glibenclamide
- Glipizide
- Glucilazide
- Glimepiride

While first generation SUs chlorpropamide and tolbutamide are obsolete, second generation SUs are still mainstay of pharmacotherapy for managing T2DM in India.

**Mechanism of action**

Provides a brisk release of insulin from pancreas → binding to the sulfonlylurea receptor on the surface of the b-cell → inhibit potassium efflux → depolarizing the b-cells and facilitating insulin release.

**Characteristics**

The rate of insulin secretion at any glucose concentration is increased Sulfonlylureas primarily augment the 2nd phase of insulin secretion with little effect on the 1st phase. Presence of at least 30% function of B cells is essential for their action.

**Minor actions**
- Reduction of glucagon secretion probably by increasing insulin
- Hepatic degradation of insulin is slowed.
- Extrapancreatic action
- They sensitize the target tissues mainly liver to the action of insulin.
- There is increase in number of insulin receptors and post receptor action i.e. improving translation of receptor activation

**Current place in the therapy**

- They are effective both as monotherapy and in combination with other hypoglycemics
- Sulfonylureas are the most potent oral agents available for managing T2DM
- Average reduction of glycosylated hemoglobin (HbA1C) of around 1–2% which is equivalent with metformin and greater than other oral hypoglycemic agents.22
- As add on therapy with metformin, SUs treatment has been shown to cause a greater reduction of HbA1c than thiazolidinedione’s and a similar effect as insulin.23

**Controversies with sulfonylureas**

Despite a documented efficacy, low cost and decades of clinical experience backing their usage, SUs in recent times have raised some concerns which tend to limit their use in treating T2DM patients.

- Patients on SU monotherapy experience a progressive loss of glucose control.
- Documented side effects of weight gain and risk of hypoglycemia.
- Increased cardiovascular risk associated with SU usage.

**INCRETIN- MIMETICS**

**GLP-1 analogues or mimetics**
Agonists of the GLP-1 receptor.

- Exenatide
- Liraglutide (Currently available)
- Exenatide LAR (sustained release; once weekly)
- Tassoglutide (trials halted due to hypersensitivity and gastrointestinal complications)
- Lixisenatide (Possible future)
- Albilglutide
- Dulaglutide

**DPP-4 inhibitor**

- Sitagliptin
- Vildagliptin
- Saxagliptin
- Linagliptin
- Alogliptin
- Dutogliptin
- Gemigliptin

**Mechanism of action**

- Glucose and other nutrients generate chemical signals 'incretins' from the gut and are more effective in invoking insulin release when given orally than i.v. which act on B cells in the pancreas to cause anticipatory release of insulin.
- The incretins involved are glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), vasoactive intestinal peptide (VIP), pancreozymincholecystokinin.
- GLP-1 is destroyed by dipeptidyl peptidase (DPP)-4, which occurs almost immediately upon secretion of GLP-1, rendering it a short half-life(<2 minutes).GLP-1 mediates its effects through receptors belonging to the G protein-coupled receptor family.
- As a therapeutic principle, GLP-1 possesses some remarkably attractive properties [24]
  a. Stimulates insulin secretion & suppresses glucagon secretion
  b. Delays gastric emptying and acid secretion: reduces food intake and facilitates weight loss.
  c. Enhances insulin, GLUT 2 and glucokinase gene expression

**Exenatide**

This molecule was originally isolated from the saliva of the Gila monster. It is given as a twice-daily subcutaneous injection. 25,26

**Exenatide LAR (sustained release)**

LAR (once a week or once a month) preparations.

**Liraglutide**

Average HbA1c reduction seen is up to 1.6% and weight loss of up to 2.5 kg over 30 weeks. There is a warning issued toward the rare complication of pancreatitis.

**Albiglutide**

It is a long-acting GLP-1 mimetic, resistant to DPP-4 degradation. It may provide a more patient-friendly dosing profile (once-weekly or less frequent)

**Lixisenatide**

Very potent and selective GLP-1R agonist. It causes significant weight loss &demonstrates the best efficacy-to-tolerability ratio.

**Adverse drug reactions**

- Gastrointestinal Effects- Delayed gastric emptying can cause discomfort, nausea and vomiting; diarrhoea may also occur. Although these effects tend to diminish with time, and most patients find them tolerable.
- Antibody Formation- Low-titre anti-exenatide antibodies were common with exenatide treatment, but had no apparent effect on efficacy. 27
- Structural changes in the human pancreas- Increases in pancreatic weight, presumably mainly due to overgrowth of exocrine tissue, have been reported in some rodent models of diabetes.
- Carcinoma of the Pancreas- Subclinical increases in pancreatic enzymes, and more rarely in severe acute pancreatitis. Subclinical increases in pancreatic enzyme levels are regularly seen in those on GLP-1 based therapies, their significance is unknown. low grade inflammation and high levels of GLP-1 activity will predispose to the development of pancreatic cancer.
- Thyroid cancer- In carcinogenicity studies with liraglutide, C cell tumours were observed in thyroid tissue of mice and rats, and C-cells were observed to proliferate in response to GLP-1 agonist therapy [28,29]

**DPP-4 INHIBITORS (GLIPTINS)**

Oral DPP4 inhibitors increase the availability of endogenous GLP1, thus enhancing glucose-induced insulin secretion and inhibiting glucagon release. These agents have no effect on gastric emptying and do not affect body weight. 30,31

**Advantages of Using DPP – 4 Inhibitors**

- As Monotherapy- Fasting glycemia reduction-approximately 18 mg/dl,Post-prandial glycemia reduction– approximately 25 mg/dl, HbA1c reduction– approximately 0.75%, equally efficacious
as compared to other antidiabetic agents with added advantage of lesser incidence of hypoglycemia and being weight neutral.\textsuperscript{32}

- As Initiation Therapy- Can be safely coupled with Metformin as an Initiation therapy as per the latest guidelines. Insulin dose can be reduced if given with glitins.
- Combination therapy- Can be given safely with anti-hypertensives, anti-hyperlipidemics and antibiotics
- Cardiac friendly profile- Preclinical studies have suggested endothelial benefit, anti-atherosclerotic effects and blood pressure lowering effects.
- Safe in Hepatic Insufficiency.
- Safe in Renal Insufficiency.
- Well Tolerated in most people with not much significant adverse event profile.

Recent data is emerging that in addition to improving beta-cell health & improve insulin resistance and plasma levels of triglyceride-rich lipoproteins.\textsuperscript{33,34,35}

**Adverse effects**

- Dipeptidyl peptidase 4 inhibitors were generally well tolerated in most studies.
- Non-selective inhibition of other members of the DPP-4 gene family suggested an increased risk of nasopharyngitis, headache, urinary tract infection.
- Although rare an increased incidence of extremity pain was seen with DPP-4 inhibitors.

**MEGLITINIDE ANALOUGES**

**Repaglinide and Nateglinide**

Repaglinide, the first member of the group, was approved for clinical use in 1998. A relatively new class of insulin secretagogues. They usually tend to be less potent than sulfonylureas, lowering A1C by ~1-1.5 percentage points.\textsuperscript{36}

**Mechanism of Action**

Modulate B-cell insulin release by regulating potassium efflux through the potassium channels.

**Indications**

- Post prandial hyperglycemia.
- Repaglinide is approved as monotherapy or in combination with biguanides.

**Advantages**

- It has a very fast onset of action but the duration of action is 5-8 hours.

**Disadvantages**

- This drug should be used cautiously in individuals with renal and hepatic impairment.
- Cost is a major disadvantage & considerably more expensive than sulfonylureas.
- Frequent dosing may also adversely affect patient compliance.

**Nateglinide**

It is the latest insulin secretagogue available clinically available and is a D-Phenylalanine Derivative.

**Mechanism of Action**

Stimulates very rapid and transient release of insulin from B cells through closure of the ATP-sensitive K+ channel.

**Indications**

- Special role in the treatment of individuals with isolated postprandial hyperglycemia.
- It is efficacious when given alone or in combination with non-secretagogue oral agents.

**Advantages**

- The overall duration of action is less than 4 hours.
- The incidence of hypoglycemia may be the lowest of all the secretagogues.
- Safe in individuals with very reduced renal function.

**Disadvantages**

- It has minimal effect on overnight or fasting glucose levels.

**SGLT-2 Inhibitors**

- Dapagliflozin
- Canagliflozin
- Empagliflozin
- Ipragliflozin
- Tofogliflozin
- Luseogliflozin
- Ertugliflozin

**Mechanism of Action**

SGLT-2 inhibitors suppress renal glucose reabsorption and thereby increase urinary glucose elimination. Hyperglycemia is thus reduced. However, SGLT-2 inhibitors inhibit reabsorption of only ~30-50% of the glucose filtered by the kidney.
Advantages

Acting independently of insulin, these agents should not confer a risk of hypoglycaemia. Can be employed as monotherapy or in combination with other agents.

Adverse drug reactions

- Urinary Tract Infections- The most common side effect for this drug class; increased glucose in the urine can worsen yeast or bacterial infections commonly associated with diabetes.37
- Hypotension- This is due to intravascular volume contraction. Seen in nearly 2% of patients taking molecule. Most common in patients with impaired renal function, elderly or on patients on drugs that interfere with the RAS system like ACE inhibitors, ARBs.
- Dehydration- Mainly in elderly, or if combined with diuretics
- Hyperkalemia
- Increased LDL (dose related)
- Ketoacidosis
- Increased risk of bone fractures- Has been observed with canagliflozin therapy and fractures have been observed as early as 12 weeks after starting canagliflozin

A -GLUCOSIDASE INHIBITORS (AGIS)

Acarbose and Voglibose

Mechanism of action

Acarbose is a complex oligosaccharide which reversibly inhibits a-glucosidases, the final enzymes for the digestion of carbohydrates present in the brush border of small intestine mucosa. Thereby AGIs slows down and decreases digestion and absorption of polysaccharides and sucrose and used in the treatment of patients with type 2 diabetes or impaired glucose tolerance.

Antidiabetic use

- It is a mild anti hyperglycaemic not a hypoglycaemic.
- It may be used as an adjuvant to diet with or without a sulphonylurea.
- Regular use tends to lower HbA1c by 0.5–0.8%, weight and serum triglyceride to a moderate level.
- long-term acarbose in prediabetes reduces occurrence of T2DM as well as hypertension and cardiac problems.
- Postprandial hyperglycaemia is reduced without increasing insulin levels.

Adverse Drug Reaction

It is minimum absorbed, but produces flatulence and abdominal discomfort.

THIAZOLIDINEDIONE DERIVATIVES

- Troglitazone
- Rosiglitazone
- Pioglitazone

Troglitazone was introduced in 1997 but withdrawn from the market in 2000 due to increased risk of hepatic necrosis.

Mechanism of Action

These are synthetic ligands for peroxisome proliferative-activated receptor (PPARγ) and improves Insulin sensitivity.38 PPARγ is mainly expressed in adipose tissue & increases insulin sensitivity by acting on adipose, muscle, and liver to increase glucose utilization and decrease glucose production.39 Thiazolidinediones have also been shown to exert potent antioxidant effects. Various thiazolidinediones have differential effects on PPAR-gamma and PPAR-alpha. Pioglitazone exerts some PPAR-alpha effects. This may account for the different effects that pioglitazone and rosiglitazone have on lipids

Adverse drug effects

- Peripheral edema and weight gain-Thiazolidinediones also have been reported to cause anemia, weight gain, edema and plasma volume expansion.40 These drugs should not be used in patients with New York Heart Association class 3 or 4 heart failure. Proposed mechanisms includes expansion of plasma volume following a reduction in renal sodium excretion, or a direct effect to increase vascular permeability
- Hepatotoxicity- Troglitazone has been withdrawn from market because of hepatotoxicity. Second generation thiazolidinediones appear to be less severe.
- Asymptomatic hyponatraemia
- CHF- CHF induced by TZD administration is thought to be due to renal sodium retention.41

Contraindications

- Abnormal cardiac function.

Obese hypertensive with cardiac diastolic dysfunction are at greatest risk for fluid retention.

Commonly seen co-morbidities in diabetes mellitus

- Coronary artery heart disease (CAD)

Metformin

Should be avoided in patients whose CAD is complicated by acute or unstable HF because of the risk of lactic acidosis,
Pioglitazone

Should be avoided in patients whose CAD is complicated by HF because of the risk of fluid retention.48

Secretagogues

Include the sulfonylureas and the non-sulfonylureaglinides.

Certain sulfonylureas (eg, glyburide) may impair ischemic preconditioning and are probably best avoided in patients with active coronary insufficiency.49,50

Insulin

Can be added to or substituted for oral agents at any point in the disease course. When more advanced regimens are used, insulin secretagogues traditionally

Secretagogues

This include the sulfonylureas and the non-sulfonylureaglinides. Certain sulfonylureas (eg, glyburide) may impair ischemic preconditioning and probably are best avoided in patients with active coronary insufficiency.

Metformin

Is no longer contraindicated in this setting and may be used cautiously, but only in stable, compensated HF patients with normal renal function and acid/base status.51,52

Insulin

Can be added to or substituted for oral agents at any point in the disease course. When more advanced regimens are used, insulin secretagogues traditionally are discontinued. Because of the sodium-retaining properties of insulin, the lowest effective dose should be used, and the dose should be titrated carefully.60

Table 2: Drugs in pipeline for T2DM.

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Mechanism of action</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>11β-hydroxysteroid dehydrogenase type 1 inhibitors</td>
<td>Inhibit an enzyme responsible for activating cortisone to cortisol, which minimizes antiglycemic effects of cortisol</td>
<td>Low potential for hypoglycemia. All drugs currently in phase 2 clinical trials</td>
</tr>
<tr>
<td>Glycogen phosphorylase inhibitors.44</td>
<td>Inhibit enzymes responsible for hepatic gluconeogenesis</td>
<td>Still very early in development. Oral agents have shown promising results in animals and humans inhibitors</td>
</tr>
<tr>
<td>Glucokinase activators.45</td>
<td>Activate key enzyme to increase hepatic glucose metabolism</td>
<td>Several drugs are currently in phase 2 clinical trials</td>
</tr>
<tr>
<td>Glucagon-receptor antagonists.46,47</td>
<td>Block glucagon from binding to hepatic receptors, thereby decreasing gluconeogenesis</td>
<td>Low potential for hypoglycemia</td>
</tr>
</tbody>
</table>

CONCLUSION

Currently available drugs provide less than fully adequate therapy for the majority of patients with diabetes mellitus. As a result, they have greater morbidity and mortality compared with age-matched non-diabetics. Despite the fact that a variety of antidiabetic agents are available for the treatment T2DM patients, there are shortcomings in diabetes treatment at present and the search for optimal therapy is ongoing. Putting aside common side-effects, such as weight gain and hypoglycaemia, current diabetes therapies do not address the key driver of this condition, namely b-cell dysfunction, and do not alter the progressive nature of the insulin secretory deficit. The challenge of treating type 2 DM grows by the day as the number of patients increase. Therefore, a good understanding of the available treatment modalities is of great value and development of new antidiabetic drugs should not only address blood glucose levels, but also aim to halt disease progression, restore b-cell function and, in the long run, reduce T2DM-associated complications, such as cardiovascular risks.

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