

ORAL HYPOGLYCAEMIC AGENTS IN THE MANAGEMENT OF TYPE II DIABETES MELLITUSDurgaprasad M. Kabade¹, Anand Koppad², Ameet Khatawkar³, Savitri D. Kabade⁴, Afaq Ahmed⁵¹Associate Professor, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli.²Assistant Professor, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli.³Assistant Professor, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli.⁴Associate Professor, Department of Anaesthesia, Karnataka Institute of Medical Sciences, Hubli.⁵Post Graduate, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli.**ABSTRACT****OBJECTIVES**

Diabetes is fast gaining the status of a potential epidemic globally. The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014, the rise seen more rapidly in developing and under developed countries. Type 2 Diabetes Mellitus (T2DM) being the most common type, accounting for an estimated 85-95% of all diabetes cases. Diabetes remains a major cause of blindness, renal failure, and cardiovascular events including heart attacks, stroke and limb amputations.¹ Being an heterogeneous disorder, many adults with T2DM have difficulty controlling their blood sugar levels and associated complications as most of available antidiabetic agents aim to achieve only normoglycaemia and relieve diabetes symptoms, such as polydipsia, polyuria, weight loss, ketoacidosis while the longterm goals to prevent the development of or slow the progression of longterm complications of the disease is often unaddressed, therefore, there remains, a significant unmet demand for new agents that will help diabetic patients achieve treatment targets without increasing the risk for weight gain or hypoglycaemia. Among the new classes of oral agents, SGLT-2 inhibitors and mTOT insulin sensitisers appear to hold some good promise. However, recent articles published describing its adverse effect profile of SGLT-2 inhibitors had put a question mark on its utility. In this article, we have reviewed the plethora of available OHAs along with the newer OHAs for managing T2DM optimally.

KEYWORDS

Oral Hypoglycaemic Agents, Type 2 Diabetes, Secretagogues, Insulin Sensitisers, Incretins, DPP4 Inhibitors, SGLT-2 Inhibitors, mTOT Insulin Sensitisers.

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INTRODUCTION: Despite therapeutic advances, the incidence and prevalence of diabetes mellitus continue to surge.^{1,2,3} Type 2 Diabetes Mellitus (T2DM) accounts for an estimated 85-95% of all diabetes cases. Being a heterogeneous disorder, characterised by defects in insulin secretion and insulin sensitivity,⁴ the optimal treatment of hyperglycaemia in T2DM remains a major clinical challenge. Although very tight glycaemic targets (HbA_{1c} of 6.5%) can be met using currently available agents, it is often at the expense of side effects, particularly increases in body weight and hypoglycaemia, therefore, there remains a significant unmet need for new agents that will help diabetic patients reach treatment targets, particularly if this can be achieved without increasing the risk for weight gain or hypoglycaemia.

Adequate glycaemic control, a critical factor in reducing longterm micro- and macrovascular complications.⁵ in patients with T2DM, is often being achieved with oral hypoglycaemic agents like insulin sensitisers (e.g. thiazolidinediones; TZDs), insulin secretagogues {e.g.

sulphonylureas (SUs) and meglitinides} and external insulin delivery (insulin analogues).⁶

Among the new classes of oral agents that are currently available, are those that induce renal glycosuria by targeting the renal Sodium-Glucose Transporter-2 (SGLT-2) appear to hold real promise. However, recent articles published describing its adverse effect profile have put a question mark on its utility. In this article, we have discussed the currently available OHAs along with the recently available SGLT-2 inhibitors and upcoming mTOT Insulin sensitisers.

Review Literature:**Currently Available OHA for Treating Type 2 DM****These Include:**

- Insulin Sensitisers (Biguanides, Thiazolidinediones).
- Insulin Secretagogues (Sulfonylureas).
- Insulin secretagogues (Non-Sulfonylureas, Meglitinides).
- Alpha Glucosidase Inhibitors.
- DPP4 Inhibitors.
- Incretins. (Amylin Agonists/GLP-1 Agonists).

Newer Agents:

- SGLT-2 Inhibitors.
- mTOT Insulin Sensitisers.

Insulin Sensitisers: Insulin sensitisers are the drugs that address the core problem in Type 2 Diabetes—Insulin Resistance.

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Biguanide: Metformin is the only drug of Biguanide class, available, with significant credibility, since past six decades, till date. Phenformin and Buformin were withdrawn from many countries, including India due to high risk of lactic acidosis.^{7,8,9} Metformin activates AMP-Kinase, an intracellular signal of depleted cellular energy stores, implicated in stimulation of skeletal muscle glucose uptake and inhibition of hepatic gluconeogenesis. Metformin improves islet cell responsiveness to a glucose load through the correction of glucose toxicity.¹⁰ and improves peripheral glucose utilisation by enhancing muscle uptake of glucose, increased insulin receptor tyrosine kinase activity, and increased glut-4 translocation and transport activity. Metformin also decreases hepatic gluconeogenesis by inhibition of key enzymes in this pathway and mitochondrial depletion of the energy necessary for gluconeogenesis.¹¹

Besides its therapeutic and preventive antglycaemic efficacy, other advantages include, Insulin Sensitisation, modulation of functions of endothelium and non-alcoholic fatty liver disease, anti-inflammatory.¹² and anti-neoplastic potentials,¹³⁻¹⁹ lipid lowering benefits, weight neutral/reduction, cardiovascular protection and above all cost effective. Safety and efficacy of metformin made it the cornerstone of monotherapy, Joint guidelines from AACE and ACE recommend, metformin be initiated as first line monotherapy unless contraindicated due to GI intolerance, coexisting lactic acidosis, renal or hepatic disease.²⁰ prior to surgery, up to 48 hours after IV contrast. It is equally efficacious in normal weight, overweight, and obese Type 2 Diabetic patients.²¹ UKPDS study reported, metformin reduced cardiovascular events.²² an effect that may be mediated via adenosine monophosphate-activated protein kinase-endothelial nitric oxide synthase (eNOS)-mediated signalling.²³ Metformin reduces diabetes related complications in type 2 DM. It does not typically cause weight gain and in some cases causes weight reduction.

Metformin is also used as dual/triple therapy, extensively in combination with several other classes of OHA. The safety and efficacy of SU plus metformin, a commonly prescribed combination, is well documented.²⁴ Many studies investigated association between combination therapy of metformin with SUs and the risk of cardiovascular disease and mortality with conflicting results. While some studies reported an increased risk of all-cause cardiovascular disease mortality.^{22,25} others have reported no association.^{26,27} Recent meta-analyses by Rao et al. have shown that this combination therapy significantly increased the relative risk of cardiovascular hospitalisation or mortality (Fatal and Nonfatal events), however, no statistically significant effects were observed on cardiovascular disease mortality or all-cause mortality.²⁸ Despite being most widely used OHA in the world, metformin may reach a plateau of effectiveness due to progressive β -cell failure.^{29,30} Availability of endogenous and exogenous Insulin determines effectiveness of metformin which in turn limits tight glycaemic control, as the disease progresses.³¹ It is important to evaluate the benefit versus risk prior to treatment decisions.

Thiazolidinediones: (Glitazones) Thiazolidinediones (TZDs) are synthetic ligands for the Peroxisome Proliferation Activating Receptor γ (PPAR γ), a group of nuclear hormone receptors involved in the regulation of genes related to glucose and lipid metabolism.³² PPAR γ , mainly expressed in adipose tissue, improves insulin sensitivity, an effect poorly understood, but thought to be due to redistribution of lipid from ectopic sites to subcutaneous adipose tissue.^{33,34} Thiazolidinediones have been shown to preserve or improve β -cell function and reduce insulin resistance in patients with T2DM while on active treatment.³³⁻³⁷ and adult-onset latent autoimmune diabetes; however, it may cause weight gain and peripheral oedema.³⁵

Rosiglitazone, Pioglitazone and Troglitazone, major drugs of this class, were found to reduce the risk of incident diabetes in subjects with prediabetes by more than 60%.^{36,37} Dosed once daily, Rosiglitazone 4-8 mg/day and Pioglitazone 15-45 mg/day, absorbed within 2-3 hours, with bioavailability unaffected by food, they require presence of insulin for pharmacological activity and are not indicated to treat Type 1 Diabetes. Having slow onset of action, they achieve maximal effects on glucose homeostasis over 1-3 months.^{38,39}

Troglitazone (Rezulin), was taken off the market due to an increased incidence of drug-induced hepatitis.⁴⁰ France and Germany banned Pioglitazone after Proactive study published in 2005 suggesting the drug could raise the risk of bladder cancer.⁴¹ Many further studies, including observational studies, were further analysed; however, results remain in conflict.^{42,43} Sale of Rosiglitazone was restricted in the US and withdrawn from Europe as some studies suggested an increased risk of cardiovascular events.⁴⁴ Initial reports of increased CV events associated with TZDs have been refuted by several prospective randomised studies.^{45,46} and FDA, on reanalysis, lifted the restrictions in 2013.^{45,46} Lobeglitazone has been, approved for use in Korea. Experimental, failed and non-marketed other agents of this class include : Ciglitazone, darglitazone, englitazone, netoglitazone, rivoglitazone. Weight gain, increased incidence of fluid retention, heart failure and increased risk of fracture (decreased bone mineral density, especially in women) associated with the use of TZDs, have raised controversies regarding its use.⁴⁷ Fluid retention is exacerbated by insulin and may be associated with macular oedema.⁴⁸

Insulin Secretagogues: Secretagogues, a class of agents that achieve their hypoglycaemic effects through stimulating insulin release, are classified as:

- Insulin Secretagogues (Sulfonylureas).
- Insulin Secretagogues (Non-Sulfonylureas, Meglitinides).

The secretagogue agents have been studied extensively as monotherapy and in conjunction with other class of oral agents, including Alpha-Glucosidase Inhibitors, Biguanides, and Thiazolidinediones, for the treatment of Type 2 Diabetes.⁵

Sulfonylureas: Chemist Marcel Janbon and co-workers, while studying sulfonamide antibiotics in 1942,⁴⁹ observed that the compound sulfonylurea induced hypoglycaemia in animals.⁵⁰ which lead to discovery of Sulfonylureas. Since 1950s, Sulphonylureas have long been established in the treatment of T2DM, and were the first oral anti-diabetic medications to be introduced into clinical practice.⁶ They are still widely used and are the second-line recommended choice of oral hypoglycaemic treatment after metformin.⁵¹

Sulfonylureas bind to a specific site on the cell, K_{ATP} channel complex (The Sulfonylurea Receptor, SUR) and inhibit its activity, causing cell membrane depolarisation and the cascade of events leading to insulin secretion from pancreatic beta cells, and may also improve insulin resistance in peripheral target tissues.⁵² The K_{ATP} channel, actually a hetero-octamer, composed of SUR1 and Kir6.2 subunits, is the site of action of several classes of drugs. ATP binds to and inhibits Kir6.2; sulfonylureas and meglitinides bind to and inhibit SUR1; All 3 agents thereby promote insulin secretion, Diazoxide and ADP-Mg²⁺ (Low ATP) bind to and activate SUR1, thereby inhibiting insulin secretion while Incretins enhance insulin secretion.⁵²

Classification of Sulfonylureas:

- First Generation Drugs: Carbutamide, acetohexamide, chlorpropamide, and tolbutamide, metahexamide.
- Second Generation Drugs: Glibenclamide, glipizide, gliclazide, glyburide.
- Glibornuride, gliquidone, glisoxepide, and glycopyramide.
- Third Generation Drugs: Glimepiride.
- Fourth Generation Drugs: (Light-Dependent) Drugs include JB253 and JB558.

Although SU therapy effectively lowers blood glucose concentrations (Average decrease in FPG of 2–4 mmol/L, accompanied by a decrease in HbA_{1c} of 1–2%) by stimulating insulin secretion from β -cells, treatment with SUs is associated with a progressive linear decline in β -cell function.^{35,53} Eventual inability to maintain glycaemic control reflects an advanced stage of β -cell failure as Sulfonylureas are ineffective where there is absolute deficiency of insulin production such as in type 1 diabetes or post-pancreatectomy.³⁵ Not all patients on sulfonylurea therapy will have an adequate response. Primary or Secondary failure have been observed with sulfonylurea therapy.

Primary failure results when a patient exhibits an initial poor response to sulfonylurea therapy (a decrease in FPG levels of less than 20 mg per dL [1.1 mmol per L]), while secondary failure results when the patient responds well to treatment initially (a decrease in FPG of greater than 30 mg per dL [1.7 mmol per L]), but eventually the treatment fails to maintain adequate control.⁵⁴

In general, first-generation SUs are rarely used nowadays due to their severe side-effects like hypoglycaemia or even coma and binding to cardiac receptors, resulting in failure of coronary vasodilatation and subsequent deleterious cardiac effects due to low specificity

of the biological action, delayed time of onset and the long duration of the effect.⁵⁵ Second-generation SUs exhibit a safer and better biological profile, as they addressed the issues of improvements of SU-induced hypoglycaemia and cardiovascular side-effects. achieved by selective binding and a rapid onset of action.⁵⁶ Small doses of sulfonylurea (e.g., 0.5 to 3 mg of glimepiride or 2.5 mg to 10 mg of extended-release glipizide) are remarkably effective, particularly in patients receiving concomitant insulin-sensitizing therapy, and are almost uniformly well tolerated. Extended-release glipizide and glimepiride are preferred agents as they can be given once daily in most patients and involve a relatively low risk of hypoglycaemia and weight gain. Triple therapy of sulfonylureas, a biguanide (M) and a thiazolidinedione is generally discouraged.

Glyburide is being tried intravenously,⁵⁷ as a treatment for acute stroke, traumatic brain injury and spinal cord injury based on the identification of a non-selective ATP-gated cation channel which is upregulated in neurovascular tissue during these conditions and closed by sulfonylurea agents.^{58,59}

Non-Sulfonylureas:

K_{ATP} Channel Modulators: Meglitinides/ D-Phenylalanine Analogues.

Meglitinide analogues, benzoic acid derivatives, structurally unrelated to the sulfonylureas, are a different class of insulin secretagogues, stimulates prandial insulin release by inhibiting ATP-sensitive potassium channels of the beta-cell membrane via binding to a receptor distinct from that of sulphonylureas (SUR1/KIR6.2).⁶⁰ Meglitinides have a very short onset of action and a short half-life.⁶¹

Repaglinide, first clinically available insulin secretagogue, specifically enhances early-phase prandial insulin response by increasing the sensitivity of β -cells to elevated glucose levels, producing a greater insulin release under hyperglycaemic conditions.^{62,63} In vitro, Repaglinide increases insulin release from β -cells only in the presence of glucose (As seen in the presence of 5 and 10 mmol/L of glucose), thus carries low risk of hypoglycaemia, whereas glibenclamide stimulates insulin secretion in the absence of glucose.⁶⁴ hence greater risk of hypoglycaemia. In vitro Repaglinide is five-times more potent than Glibenclamide in stimulating insulin secretion, with half-maximal stimulation observed at 40 and 200 nmol/L, respectively.⁶⁴

Taken orally immediately before a meal, Repaglinide has shown to reduce postprandial hyperglycaemia. Suitable for life style with unpredictable or missed meal, or in elderly due to low risk of hypoglycaemia, particularly, when other agents may be contraindicated. Repaglinide has been shown to be associated with 60% fewer hypoglycaemic episodes compared with a second-generation SU.⁶⁵ Nateglinide, another drug of same class, is a derivative of phenylalanine and is structurally distinct from both Sulfonylureas and the Meglitinides. Its fleeting interaction with SUR1 produces a more rapid but less sustained insulin release compared to other available OHAs, which makes its effect in lowering postprandial glucose, quite specific, hence is mainly used to reduce postprandial hyperglycaemia.

Its most effective in a dose being 120 mg, 1-10 minutes before a meal. When combined with Metformin.⁶⁶ while Metformin reduces basal plasma glucose levels, Nateglinide controls post-prandial peaks. It can also be used in combination with pioglitazone or rosiglitazone. Mitiglinide, the third drug of this class, also exhibits a rapid onset and short duration of action, mimicking a physiological pattern of insulin release in non-diabetic people.⁶⁷ thus mainly targets post-prandial hyperglycaemia.⁶⁷ This drug modestly decreases HbA_{1c}, post-prandial hyperglycaemia, oxidative stress and inflammatory markers associated with post-prandial hyperglycaemia. Mitiglinide is well tolerated. However, it has not gained approval from the FDA.

α -Glucosidase Inhibitors: Alpha-Glucosidase Inhibitors (AGI) delay break down of complex carbohydrates by inhibiting action of enzyme glucosidase in the brush border of upper part of small intestine thereby reduce intestinal absorption of carbohydrates like starch, dextrin and disaccharides, and blunts the rate of rise of postprandial plasma glucose, without increasing insulin levels. These drugs also increase Glucagon Like Peptide-1 (GLP-1) levels which may contribute to their glucose lowering effects.⁶⁸ Another reported advantage of α -Glucosidase Inhibitors is reduction of postprandial glucose without inducing hypersecretion of insulin.^{69,70} an effect, desirable in treatment of NIDDM patients for two reasons: 1) Hyperinsulinemia may promote development of coronary artery disease.^{71,72} and 2) Hypersecretion of insulin may result in exhaustion of the pancreatic β -cells.^{73,74}

The efficacy of α -Glucosidase Inhibitor on insulin sensitivity remains controversial.^{75,76} AGIs primarily target post prandial hyperglycaemia and seldom cause hypoglycaemia as they do not increase insulin secretion; however, increased delivery of carbohydrate to the colon often results in increased gas production and gastrointestinal symptoms, such as flatulence and diarrhoea.^{68, 77} In case of hypoglycaemia while on α -Glucosidase, glucose should be used to treat hypoglycaemia as digestion of sucrose or more complex sugars is inhibited with these agents.

Acarbose, emiglitate, miglitol and voglibose of this class are available. All AGIs act on α -glucosidases. However, acarbose is minimally absorbed and most effective in inhibiting glucoamylase, whereas miglitol is a more potent inhibitor of disaccharide-digesting enzymes.⁶⁸ In the STOPNIDDM trial, Acarbose demonstrated 25% reduction in the progression of impaired glucose tolerance to T2DM and significant reduction in the risk of developing for cardiovascular disease.⁷⁸ Miglitol is cleared almost entirely by the kidney, and dose reductions are recommended for patients with creatinine clearance <30 mL/minute. Acarbose can decrease absorption of digoxin while Miglitol can decrease absorption of propranolol and ranitidine.

Voglibose is a new α -glucosidase inhibitor having similar actions as other drugs of the same class, however, Voglibose is reported to be ~2 0 to 30 times more potent than acarbose in inhibiting semipurified porcine small intestine disaccharidases.⁷⁹

Voglibose lowers the daily glycaemic excursions and inhibits overwork of the pancreatic (β -cells but has little effect on insulin sensitivity in NIDDM patients.⁸⁰

In a study comparing Metformin and Voglibose as individual drugs versus fixed dose combination (FDC) in patients with T2DM, Metformin of the Voglibose/Metformin FDC met the regulatory criteria for bioequivalence compared to coadministered individual voglibose and metformin. Both the FDC formulation and individual tablets were well tolerated and their safety profiles were not significantly different.⁸¹ Interestingly, AGIs are frequently prescribed as first-line agents in Asian countries with a diet rich in complex carbohydrates, but they are seldom prescribed in the US and Europe, where the diet is rich in protein and fat.⁶ New AGIs are being developed to improve the efficacy and safety of this class of drugs.⁸²

Incretins:

(Amylin Agonists/GLP-1 Agonists): Incretins, are the gut hormones, released in response to nutrient ingestion (Mainly glucose and fat) and exert a wide range of effects, including pancreatic insulin secretion in a glucose-dependent manner and also influence local gastrointestinal and whole-body physiology.⁸³ Two gut hormones, Glucose-dependent Insulinotropic Peptide (GIP) secreted from L-cells of the distal ileum and colon and Glucagon Like Peptide-1 (GLP-1) secreted from the K-cells in the duodenum and jejunum.⁴ were found to mediate the "Incretin Effect" (Higher Insulin

Release in Response to an Oral Glucose Challenge Compared with an Equal Intravenous Glucose Load): The two hormones equally contribute to the incretin effect and have cumulative outcomes.⁸⁴ GLP-1 receptors are expressed by cells and binding of agonists to the GLP-1 receptor activates the cAMP-PKA pathway. Incretins, having plasma $t_{1/2}$ of 1–2 minutes, are rapidly inactivated by the enzyme DPP4, thus, the natural peptide itself is not a useful therapeutic agent, hence, GLP-1 analogues exenatide and liraglutide, given subcutaneously, evade rapid clearance by DPP4 and have a long half-life. The analogues stimulate glucose-dependent insulin secretion, inhibit glucagon release, delays gastric emptying, promote early satiety, reduces food intake, and normalizes fasting and postprandial insulin secretion.

Exenatide, the first GLP-1 analogue, approved by FDA in April 2005, is a synthetic Incretin, derived from exendin-4, found in the saliva of the Gila monster lizard and has approximately 50% homology with human GLP-1.⁶ given as a subcutaneous injection twice daily, typically before meals, is rapidly absorbed, reaches peak concentrations in about 2 hrs. Clearance is primarily by glomerular filtration, with tubular proteolysis and minimal re-absorption. Exenatide, when used alone or in combination with metformin, sulfonyleurea, or thiazolidinedione, was associated with improved glycaemic control, as reflected in an ~1% decrease in HbA_{1c}.^{85,86,87} Liraglutide, a drug of this class, approved by the FDA in January 2010, has 97% homology with GLP-1 and produces dose-dependent weight loss and reduction in blood pressure in obese subjects.⁸⁸ However,

long-term liraglutide exposure in rodents was associated with thyroid C-cell hyperplasia and tumours.⁸⁹

Given as subcutaneous injection once daily, Liraglutide achieves peak levels in 8-12 hours and half-life ($t_{1/2}$) being 12-14 hours, It is not recommended as initial therapy, is indicated for adjunctive therapy in patients not achieving glycaemic control with metformin, sulfonylurea. It has minor adverse reactions like nausea vomiting, although rodent studies have shown an increase in the occurrence of benign C-cell adenomas and malignant C-cell carcinomas at supraphysiologic doses.⁹⁰ their relevance to humans is unknown. In the phase 2 and phase 3 trials of liraglutide, there were 7 cases of pancreatitis reported among the 4257 patients treated with liraglutide and only one case in the 2381 patients in the comparator group. The small number of events made it difficult to draw conclusions about causation.⁹⁰ Two more GLP-1 analogues, Albiglutide and Taspoglutide have been developed. Phase III clinical trial of Taspoglutide were halted due to serious hypersensitivity reactions and gastrointestinal side-effects.⁹¹

Pramlintide: The incretin, pramlintide, an injectable synthetic analogue of the human hormone amylin (A polypeptide secreted by pancreatic β cells) acts through specific binding to the amylin receptor in specific regions of the hindbrain, which reduces glucagon secretion, delays gastric emptying and causes decreased satiety, and has been shown to promote weight loss in morbidly obese Type 2 Diabetic patients.⁹² Pramlintide is approved for treatment of Types 1 and 2 Diabetes as an adjunct in patients who fail to achieve desired glucose control, despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin. Administered as a subcutaneous injection prior to meals, with starting dose of 15 μ g, titrated upward to a maximum of 60 μ g, in T1DM, while in T2DM, initial dose is 60 μ g and maximum, 120 μ g. Patients on pramlintide and insulin are at a higher risk of hypoglycaemia and should be instructed accordingly.⁹³

DPP-4 Inhibitors: Di-Peptidyl Peptidase 4 (DPP-4) is a serine protease, widely distributed in our body, expressed as an ectoenzyme in a circulating form on the surface of T-lymphocytes and endothelial cells. DPP-4 inhibitors prevent the degradation of native GLP-1, thereby giving rise to increased levels of this incretin. They are small molecules that can be absorbed orally. They are weight neutral and do not appear to impact gastric emptying or satiety.⁹⁴

Sitagliptin and Alogliptin, two drugs of this class, are competitive inhibitors of DPP-4, while Vildagliptin and Saxagliptin bind the enzyme covalently causing a greater than 2-fold elevation of plasma concentrations of active GIP and GLP-1 and are associated with increased insulin secretion, reduced glucagon levels, and improvements in both fasting and postprandial hyperglycaemia. The recommended dose of Sitagliptin is 100 mg once daily. The recommended dose of Saxagliptin is 5 mg once daily, when used as monotherapy in T2DM patients, reduced HbA_{1c} levels by an average \sim 0.8% they circulate in primarily in

unbound form and are excreted mostly unchanged in the urine.

Sitagliptin and saxagliptin though approved for clinical use by the FDA, their adverse effects like pancreatitis, oliguria and severe skin reactions limits their use. Dose adjustment is required in patients with renal impairment to half the full dose, if creatinine clearance is less than 50 mL/min and further to 25 mg for Sitagliptin if the creatinine clearance is 30 mg/mL or less.⁹⁵ Sitagliptin and saxagliptin, though approved for clinical use by the FDA, their adverse effects like pancreatitis, oliguria and severe skin reactions limit their use. Dose adjustment is required in patients with renal impairment to half the full dose, if creatinine clearance is less than 50 mL/min and further to 25 mg for Sitagliptin if the creatinine clearance is 30 mg/mL or less.⁹⁵

Teneligliptin, a novel DPP-4 inhibitor, exhibits a unique structure characterised by five consecutive rings, which produce a potent and long-lasting effect, is currently used in cases showing insufficient glycaemic control even after optimal diet control and exercise and sulfonylurea- or thiazolidine -class drugs. The adult oral dose of Teneligliptin is 20 mg once daily which can be increased up to 40 mg per day. The safety profile of Teneligliptin is similar to those of other available DPP-4 inhibitors.⁹⁶ although better tolerated in patients with hepatic impairment, caution needs to be exercised while administering Teneligliptin to patients with hepatic impairment and also to those patients who are prone to QT prolongation.⁹⁷

NEWER OHAS

SGLT-2 Inhibitors: A newer modality for Glycaemic Control in T2DM.

SGLT-2 is a low-affinity, high capacity glucose transporter located in the proximal tubule in the kidneys. It is responsible for 90% of glucose reabsorption. Inhibition of SGLT2 leads to the decrease in blood glucose due to the increase in renal glucose excretion. The mechanism of action of this new class of drugs also offers further glucose control by allowing increased insulin sensitivity and uptake of glucose in the muscle cells, decreased gluconeogenesis and improved first phase insulin release from the beta cells.^{98,99} Drugs in the SGLT2 inhibitors class include Empagliflozin, Canagliflozin, Dapagliflozin, Ipragliflozin (Which has not yet been approved for use in the U.S.). At this time Canagliflozin and Dapagliflozin are the only drugs in this class, approved by the FDA for the treatment of Type 2 diabetes.

Advantages: Since the Action of SGLT-2 inhibitors is independent of insulin, hence it carries no risk of hypoglycaemia. They could be employed as mono therapy or in combination with other agents. As per their mode of action, they may be effective irrespective of degree of insulin resistance or β - cell function agents. They may also benefit due to weight loss and reduction in blood pressure resulting from the loss of glucose (Calories) in urine and glucose-induced osmotic diuresis.¹⁰⁰ leading to positive impact on cardiovascular outcomes.¹⁰¹

Safety Issues: Most common side effects for Canagliflozin, Empagliflozin and Dapagliflozin were genital fungal infections in females and UTIs. Other adverse effects due to their diuretic effects include dehydration, hypotension, dizziness and/or fainting, as well as reduced renal function, especially among elderly patients and those on diuretic therapy. Although increased incidence of urinary tract infections (UTIs) in patients on SGLT-2 inhibitors have been reported in some studies¹⁰²⁻¹¹³; however, many of these studies could not establish the causal-effect relation, while few studies have demonstrated a rate of UTIs similar to that with placebo.¹¹⁴⁻¹¹⁵ The most common side effects associated with Canagliflozin was found to be vaginal yeast infections and urinary tract infections, with female patients and uncircumcised men being at greatest risk.

The observation, that incidence of vulvovaginitis and balanitis getting approximately doubled in patients on SGLT-2 inhibitors.¹¹⁶⁻¹¹⁸ was found to be inconsistent across all studies. Furthermore, the genital infections reported in studies of SGLT-2 inhibitors have not always been confirmed by culture. The most common side effect with Dapagliflozin were genital fungal infections and UTIs. Phase 3 clinical trials of Dapagliflozin reported 9 cases of Bladder Cancer out of 5,478 patients administered Dapagliflozin (0.16%) and 9 cases of Breast Cancer out of 2,223 female patients (0.4%) were detected, compared to the placebo groups, in which 1 of 3, 156 subjects had bladder cancer (0.03%) and 1 of 1,053 female patients had breast cancer (0.09%).¹¹⁸

The number of cases was too small to establish causality. Animal studies with doses up to 100 times the clinical dosage of Dapagliflozin did not yield observations of carcinogenesis or mutagenesis. Dapagliflozin is not recommended for patients with active bladder cancer or moderate-to-severe renal impairment.¹⁰² Empagliflozin should not be used to treat patients with severe renal impairment or ESRD or who are on dialysis. Several other SGLT-2 inhibitors are currently in Phase I, II or III clinical trials; including ISIS388626, GW869682, EGT0001442, ertugliflozin, sergliflozin, ipragliflozin, empagliflozin, tofogliflozin and luseogliflozin.⁶

mTOT Modulating Insulin Sensitisers: Insulin sensitisers discovered more than 25 years ago have shown to have positive, durable effects in the treatment of diabetes. More than a decade after the discovery of the first insulin sensitisers, activation of the nuclear receptor PPAR γ was hypothesised to be the mechanism of action through which these agents improved insulin sensitivity. However, as it has been reported widely in the literature, PPAR γ is now recognised to be responsible for the dose-limiting, off-target side effects associated with currently available insulin sensitisers. The year 2010 saw a breakthrough discovery of a key protein complex located in the inner mitochondrial membrane, called mTOT (Mitochondrial Target of Thiazolidinediones), through which insulin sensitisers produce their antidiabetic effects. Presented data suggest that the mTOT protein complex connects mitochondrial metabolism to important cellular activities perturbed in age-

related metabolic diseases such as Type 2 Diabetes, including insulin sensitivity they selectively bind and modulate proteins in the mTOT complex, effecting pyruvate utilisation and resulting in improved insulin action, lipid oxidation, preservation of beta cell function, and generation of brown fat.

The two novel insulin sensitisers, MSDC-0160 and MSDC-0602 belonging to this class that underwent Phase 2 clinical studies formed the foundation of a new class of insulin sensitising compounds called mTOT Modulators. The phase IIB clinical trial, in 258 patients with type 2 diabetes, completed a 12-week protocol with 50, 100, or 150 mg of MSDC-0160 (an mTOT modulator), 45 mg pioglitazone HCl (A PPAR- γ agonist), or a placebo, showed that the two active treatments lowered fasting glucose to the same extent. Decrease in HbA1c with the two higher doses of MSDC-0160 were not different from those associated with pioglitazone. By contrast, fluid retention as evidenced by reduction in haematocrit, red blood cells, and total hemoglobin was 50% less in the MSDC-0160-treated groups.

A smaller increase in high-molecular-weight (HMW) adiponectin was observed with MSDC-0160 than with pioglitazone, suggesting that MSDC-0160 produces less expansion of white adipose tissue. Thus, mTOT modulators may have glucose-lowering effects similar to those of pioglitazone but without the adverse effects associated with PPAR- γ agonists.¹¹⁹

Conclusions and Future Directions: Achieving target glycaemic goals in T2DM continues to be a tough clinical challenge, despite availability of variety of anti-diabetic agents, because of their limitations. Although recent therapeutic advantages have slightly eased the burden of managing the disease with the plethora of oral hypoglycaemic agents available for managing T2DM, which can be used optimally with better understandings of their potential benefits and adverse effects. Emergence of SGLT-2 Inhibitors and novel mTOT Modulating Insulin sensitisers as a newer modality for treating T2DM appear to hold promises to provide significant benefits to the patients with T2DM, nevertheless, the search for optimal therapy remains unfulfilled, as the currently available agents have failed to address the basic pathology of disease, β -cell dysfunction and its progressive nature, hence the future developments need to be directed towards them.

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