Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20130102

Review Article

Newer drugs in the management of diabetes mellitus

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Received: 2 November 2012
Accepted: 11 December 2012

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ABSTRACT

Modern life style with present days technological advances have made human life sedentary. This is causing increasing prevalence of obesity and physical inactivity amongst population. The number of cases of diabetes worldwide in the year 2000 among adults 20 years of age is estimated to be 171 million in recent reports and is said to rise to more than 300 million by 2025. The raised plasma glucose levels give rise to complications in the form of microvascular and macrovascular complications diminished quality of life with reduced life expectancy. The currently available drugs used in the management of type II DM are not completely satisfactory in regard of controlling blood glucose level, many of the times they are associated with undesirable side effects. Hence there is continuous ongoing work in development of newer drugs, which are safe, efficacious and potent as well as free of undesirable effects such as sustained hypoglycaemia. Fortunately there are newer drug, few of them approved while other still knocking the door from the classes of drug such as GLP-1Mimetic, DPP-4 Inhibitors and others. Here we have tried to cover them in brief.

Keywords: GLP-1 Mimetics, DPP-4 Inhibitors, SGLT-2 Inhibitors, Dual PPAR Agonist, Amylin Mimetics

INTRODUCTION

Modern life style with present days technological advances have made human life sedentary. This is causing increasing prevalence of obesity and physical inactivity amongst population. The International Diabetes Federation (IDF) also reported that the total number of diabetic subjects in India is 41 million in 2006 and that this would rise to 70 million by the year 2025. The number of cases of diabetes worldwide in 2000 among adults 20 years of age is estimated to be 171 million in recent reports[1] and is said to rise to more than 300 million by 2025.

Developing countries like India harbouring mixed population strata i.e. both high and low economic group may face major problems because this will place tremendous burden on their health care system. Though the medications available currently for the management of diabetes satisfactorily control the blood sugar levels, they are associated with side effects like hypoglycemia and resistance. Hence there is a need for continued search for newer group of hypoglycemic agents to deal with this pandemic.

Diabetes Mellitus is a chronic metabolic disorder characterised by a high blood glucose concentration-hyperglycemia (fasting plasma glucose > 7.0 mmol//L, or plasma glucose > 11.1 mmol/L 2hr after a meal) - caused by insulin deficiency, often combined with insulin resistance. [2] The raised plasma glucose levels give rise to complications in the form of microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (ischaemic heart disease, stroke and peripheral vascular disease) complications diminished quality of life with reduced life expectancy.

To achieve efficient control over hyperglycemia there is need to control blood sugar levels both in the basal (fasting) and postprandial state which can be done by using drugs with different mechanism of action in combinations. Both fasting and postprandial blood glucose levels need to be monitored and controlled to have maximum benefit with sufficient control. The currently available drugs used in the management of type II DM are listed in table 1.[3]

Agents that decrease fasting plasma glucose levels selectively (e.g., sulfonylurea's and metformin) or in

conjunction with lowering postprandial glucose excursions (e.g., repaglinide, pioglitazone, and rosiglitazone) lower mean Glycosylated haemoglobin A1c (HbA1c) levels by 1.5 to 2.0 percentage points. Agents that primarily lower postprandial hyperglycemia are the alpha-glucosidase inhibitors and nateglinide. These decrease mean HbA1c levels.

Recently novel categories of antihyperglycemic therapies have emerged for management of DM.

GLUCAGON LIKE PEPTIDE (GLP)-1 MIMETIC

Incretins are gut-derived peptides secreted in response to meals, specifically the presence and absorption of nutrients in the intestinal lumen. The major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). GLP-1 is produced by the neuroendocrine L cells of the ileum and colon; GIP is elaborated by K cells of the duodenum and jejunum. Both are released rapidly after meal intake; their secretion appears to be under neural control. GLP-1 and GIP stimulate insulin output from pancreatic cells in a glucose-dependent fashion as enhancement of secretion is linked to the presence of hyperglycaemia. In addition, GLP-1, but not GIP, decreases pancreatic α-cell secretion of glucagon, a hormone that augments hepatic gluconeogenesis. GLP-1 also retards gastric emptying and likely has a direct suppressive effect on central appetite centres.[4] Incretins are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), which is widely expressed in many tissues, including kidney, liver, lung, and the small intestine. Thus the cardinal physiological role of the incretin system appears to be the attenuation of postprandial glucose excursions.[5]

Notably, patients with type 2 diabetes mellitus are partially deficient in GLP-1 secretion,[6] a finding that has encouraged the development of drugs that augment GLP-1 levels or activity. Exenatide and Liraglutide are two promising agents from this class.

Table 1: Agents used currently for management of DM.[3]

Class	Agent	Mechanism of action	Site of Action	HbA1c reduction (%)	Adverse effects
Sulfonylureas	Glyburide Glipizide Glimepiride	Stimulation of Insulin release by β cells.(Insulin Secretogogues)	β cells	1 – 2	Hypoglycaemia, weight gain
Glinides	Meglitinides Nateglinide	Stimulation of Insulin release by β cells,(Insulin Secretogogues)	β cells	1 – 2	Hypoglycaemia, weight gain.
Biguanide	Metformin	Inhibition of hepatic gluconeogenesis	Liver	1 – 2	Diarrhoea, lactic acidosis, decreased B 12 levels
α-Glucosidase inhibitor	Acarbose, Miglitol	Inhibition of intestinal carbohydrate absorption	Intestine (Jejunum)	0.5 – 1	Bloating, Gas
Thiazolidinedi-ones	Rosiglitazone* Pioglitazone	Reduces peripheral insulin resistance	Muscles and Adipocytes.	1 – 1.5	Weight gain; edema; possible. bone loss in women
* Banned in India in 2011					

Exenatide

It is the first incretin modulator class encompassing the GLP-1 analogues or mimetics, which are functional agonists of the GLP-1 receptor. Exenatide shares partial homology with human GLP-1 and activates human GLP-1 receptors. It is administered as a subcutaneous injection twice daily in the dose of 5 to 10 µg.[7] The clinical trials have assessed its efficacy at lowering glucose in patients with T2DM in combination with metformin and/or sulfonylurea's.[8] In trials, Exenatide resulted in a HbA1c reduction of 1.0% compared with placebo treatment, with

the predominant effect on lowering postprandial glucose with less prominent reduction in fasting glucose.[9] Weight loss has also been demonstrated, probably because of the effects of exenatide on gastric emptying and appetite. In in-vitro and animal models, GLP-1 and its analogues are associated with proliferative effects on pancreatic cells.[10] Progressive islet dysfunction is a recognized phenomenon in T2DM and results in the eventual loss of glycemic control over time. In addition to functional abnormalities, an actual decrease in β-cell mass also has been demonstrated, likely the result of increased apoptosis combined with decreased regeneration. Therefore, any agent that alters this balance may delay or prevent the decline in insulin secretory capacity, potentially allowing a more durable effect on glucose control than conventional agents, most of which are associated with substantial therapeutic attrition over time. This hypothetical effect of the GLP-1 mimetics, however, has not yet been demonstrated in long-term clinical trials.

Side effects of exenatide include nausea and vomiting, particularly at the initiation of therapy. Recently, post marketing reports of pancreatitis occurring in exenatide-treated patients have emerged, with most patients having at least one risk factor for this condition.[7] A causal association with exenatide is not clear. Because of its glucose-dependent effect, exenatide does not increase the risk of hypoglycaemia. Exenatide is approved for use in combination with metformin, a sulfonylurea, 8 a thiazolidinedione,[9] the combination of metformin and a sulfonylurea, or the combination of metformin with a thiazolidinedione. Among patients with T2DM requiring insulin therapy, exenatide exhibits less potent HbA1c reduction compared with its combination with oral agents,[10] an expected observation because such individuals tend to be more insulin deficient with less available insulin secretory reserve. Exenatide is also effective as monotherapy, but this is not an immediately attractive option for most patients, given its method of administration.

Liraglutide

Liraglutide is another GLP-1 analogue which is 97% identical to human native GLP-1, differing only by one amino acid substitution and a glutamate-linked fatty acid side chain.[11] It had shown proven safety, efficacy, and tolerability as a glucose lowering drug, when used in type 2 diabetes mellitus.[12] Liraglutide is effective in reducing body weight, decreasing visceral fat, lowering systolic blood pressure, and improving lipid profile as well as other cardiovascular risks factors, while reducing insulin resistance. These beneficial effects on all components of the insulin resistance syndrome, or metabolic syndrome, with minimal risk of hypoglycemia, make liraglutide an attractive option for management of insulin resistance. Liraglutide has shown to reduce triglyceride levels, without affecting concentration of other lipids. While no long term data of cardiovascular outcomes is available, few studies have shown a cardio-protective effect of liraglutide.[12]

Liraglutide reaches maximum concentration after 9–12 hrs and has a half-life of approximately 13 hrs (11–15hs), thus it only needs to be administered once daily to provide full 24-hrs glycaemic control. The recommended initial dose is of 0.6 mg, progressing to 1.2 mg or up to 1.8 mg, if required.[13] Liraglutide is generally well tolerated. The most common adverse events are gastrointestinal, i.e. nausea, vomiting, and diarrhea. Hypoglycemia occurs rarely, and no major hypoglycemic events have been reported[13] with liraglutide monotherapy (LEAD-3), liraglutide + metformin (LEAD-2), and liraglutide + metformin + rosiglitazone (LEAD-4). It was also observed (in LEAD-6) that Liraglutide once a day significantly improved the glycaemic control than did exenatide twice a day suggesting that liraglutide might be a better treatment option especially when weight loss and risk of hypoglycaemia are major considerations.[14] Overall, liraglutide is effective and safe for long-term administration in patients with type 2 diabetes. On January 25, 2010, the US FDA approved liraglutide, as a single daily dose to improve glycaemic control in adults with type 2 DM.[13]

DIPEPTIDYL- PEPTIDASE-IV (DPP-4) INHIBITORS

DPP4 is an enzyme which degrades GLP1 and GIP which are the major gut hormones belonging to the family of Incretins. These incretins stimulate insulin secretion in response to raised plasma glucose concentration.[15] Thus drugs which are inhibitor of DPP4 indirectly lower the plasma glucose concentration by enhancing the levels of incretins. DPP-4 inhibitors increase effective incretin levels into a more physiological range, in contrast to therapy with GLP-1 mimetic. By inhibiting incretin metabolism, these agents not only stimulate insulin release but also reduce the glucagon secretion, thereby lowering the HbA1C and fasting as well as postprandial hyperglycaemia.[16] Drugs used from this class are Sitagliptin, Vildagliptin and Saxagliptin.

Sitagliptin

Sitagliptin is a selective inhibitor of DPP4 thus enhancing the glucose-dependent insulin secretion from the pancreas and decreases hepatic gluconeogenesis. Sitagliptin inhibits the DPP4 activity for the duration of 24 hours, hence it can be administered as a single daily dose.[17] Bioavailability of Sitagliptin is 87% with effective plasma half life of 8-14 hours. It is 38% bound to plasma proteins and undergoes CYP3A4 and CYP2C8 mediated metabolism, excreted mainly in urine.[18]

Sitagliptin was approved by the U.S. Food and Drug Administration (FDA) in October 2006, as monotherapy and as add-on therapy to either metformin or thiazolidinediones to improve glycaemic control in

patients with type 2 diabetes when diet and exercise failed to achieve the desired goals.[17] Later on in April 2007 the US FDA approved the combination product of Sitagliptin with Metformin for the patients who are not adequately controlled on either Metformin or Sitagliptin monotherapy. The combination should be administered orally twice daily with meals. DPP 4 is involved in regulation of immune functions and degradation of cytokines, hormones, neuropeptides and growth factors. Hence their inhibition runs the risk of infections.[19]

Commonest adverse effects observed with Sitagliptin are upper respiratory tract infections, urinary tract infections, headache, arthralgias, fatigue, dizziness and diarrhea. Safety and efficacy of Sitagliptin is controversial in pregnant patients due to lack of adequate data for its use in pregnancy. As it is secreted in breast milk, it should be used cautiously in nursing women. Dose adjustments are needed in patients with renal function impairment. It is also contraindicated in diabetic ketoacidosis. Hypersensitivity reactions such as anaphylaxis, angioedema and Stevens Johnson Syndrome have been reported rarely.[18]

Vildagliptin

Vildagliptin is another member of the class, having high affinity for DPP 4 thereby improving glycaemic control. Administration of Vildagliptin results in rapid inhibition of DPP 4 enzyme activity for period of 24 hours thus reducing the fasting and postprandial plasma glucose. Vildagliptin enhances the sensitivity of α- cells to glucose by increasing endogenous GLP 1 levels, resulting in reduced glucagon secretion.[20] Vildagliptin is rapidly absorbed with an absolute oral bioavailability of 85% with peak plasma concentrations observed at 1.75 hours. The rate of absorption of vildagliptin slightly decreases on co-administration with food. The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. Unlike Sitagliptin, Vildagliptin is not metabolized by cytochrome P450 enzymes.[21] Following oral administration, approximately 85% of the dose is excreted into the urine and 15% excreted in the faeces. The mean elimination half-life is approximately 2 hours after intravenous administration and 3 hours after oral administration, independent of the dose. Some of the common adverse effects are dizziness, headache, constipation and peripheral oedema. It is contraindicated in renal, hepatic impairment or hypersensitivity to either vildagliptin or any of the excipients.

Saxagliptin

Saxagliptin is approved by the US Food and Drug Administration in July 2009.[22] Saxagliptin is primarily indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type II diabetes. The recommended dose for Saxagliptin is 5 mg once-daily. Saxagliptin is extensively absorbed after oral administration. Saxagliptin is metabolized primarily by hepatic cytochrome P450 isoenzyme CYP3A4/5. It is cleared by both metabolism (21–52% of the dose is recovered in the urine as the major metabolite) and renal excretion (12–29% of the dose is recovered in the urine as the parent drug).

SODIUM-GLUCOSE TRANSPORTER (SGLT) 2 INHIBITORS

Sodium–glucose transporters (SGLT) are a family of transmembrane proteins specialized in the co-transport of sodium and glucose across different cell types. Of the six isoforms so far identified, SGLT-2 is preferentially expressed in the brush-border membrane of proximal renal tubular cells. They contribute to renal glucose reabsorption. In the kidneys, 100% of the filtered glucose in the glomerulus is reabsorbed. In case of hyperglycemia glucose is excreted in urine due to saturation of these transport channels. Inhibitors of these transport proteins enhance renal glucose excretion and consequently lower plasma glucose levels in case of hyperglycemia.[23] Hence these agents have promising role in the management of Type II diabetes. Dapagliflozin, Remogliflozin, Sergliflozin Canagliflozin are the drugs belonging to this class.

Dapagliflozin

Dapagliflozin is a potent and highly selective SGLT2 inhibitor. Ascending dose (SAD and MAD) studies with Dapagliflozin confirmed that it has a pharmacokinetic profile consistent with once-daily dosing and produces a dose-dependent increase in glycosuria in humans.[24] Dapagliflozin was rapidly absorbed after oral administration and maximum plasma concentrations were observed within 2 hrs of administration. Renal clearance of Dapagliflozin is minimal (~3–6 ml/minute) with <2.5% being excreted unchanged in the urine during a 24-hour period. In vitro studies have suggested that Dapagliflozin may be metabolized to an inactive metabolite via the glucuronosyltransferase enzyme coded for by UGT1A9.[25] Dapagliflozin had no effect on urine and serum osmalality. No treatment-related serious adverse events were reported so far. The most frequently reported treatment emergent adverse events were constipation, nausea and diarrhoea. Dapagliflozin is in development and is currently in phase 3 trials.[26]

Remigliflozin

Remigliflozin is benzylpyrazole glucoside. In various animal models it has shown reduction in the levels of fasting plasma glucose and HbA1c in a dose dependent manner. It is beneficial in reducing the post prandial hyperglycemia by enhancing urinary glucose excretion.[27] In clinical studies, conducted thus far, it has shown rapid absorption following administration with plasma half life of 120 minutes.[28] When coadministered with metformin there were no drug interactions with minimal risk of

hypoglycaemia.[28] The O- Glucoside linkages of Remigliflozin, makes it susceptible to hydrolysis by intestinal β –glucosidase, thereby reducing its plasma half life. At present, the development of this drug has been stopped in phase II clinical trials.[27]

Sergliflozin

Sergliflozin is another SGLT-2 inhibitor which has also shown dose dependent urinary glucose excretion in animal studies. In clinical trials, single oral dose of Sergliflozin produced dose dependent glycosuria under fasting as well as post prandial conditions without any influence on urinary electrolyte excretion. It has also produced significant weight reduction as compared to placebo in healthy obese individuals some minor adverse events like headache, sore throat in healthy subjects and headache, dyspepsia in diabetic patients were seen. Like Remigliflozin it shows similar pharmacokinetic profile in terms of its metabolism. Thus, though Sergliflozin has shown promising profile for the treatment of obese diabetic patients, its development of this drug has been stopped in phase II clinical trials.[29]

AMYLIN MIMETICS

Amylin is β cell polypeptide secreted along with insulin from human pancreas. It has been demonstrated that in type 1 DM as well as in late stages of type 2 DM there is deficiency of Amylin together with insulin. Amylin also reduces glucagon secretion thus lowering hepatic gluconeogenesis. They also have central satiety enhancing activity and delays gastric emptying.[30] These effects together contribute to hypoglycaemia in patients receiving insulin simultaneously. Hence insulin dose adjustment is recommended when these agents are initiated. Compared to placebo the net HbA1C reduction is moderate (0.4% to 0.6%).[31]

Pramlintide

Pramlintide is a first drug in the class of amylin mimetics for patients using insulin, reducing postprandial hyperglycemic excursions and improves overall glycaemic control with concomitant reductions in weight and insulin use. The actions of Pramlintide to slow gastric emptying, suppress inappropriately elevated postprandial glucagon secretion, and reduce food intake act collectively to limit postprandial glucose fluctuations and improve overall glycemic control.[32] It has been shown that postprandial glucose fluctuation is one of the important predictor of cardiovascular risks associated with diabetes, hence by limiting these fluctuations Pramlintide is useful to prevent morbidity associated with cardiovascular complications. Improvements in glycemic control with Pramlintide occur in the context of reductions in weight, making it an additional therapeutic choice for many insulin-using patients with overweight and obesity.[32]

Pramlintide has been approved by the US FDA for use with mealtime insulin in patients with type I and type II diabetes.[32] In the clinical trials reviewed, patients receiving Pramlintide had 0.10% to 0.67% reductions in HbAlc and 3.6 to 4.8 m mol/L reductions in 2-hour PPG levels.[33] Pramlintide had a favourable safety and tolerability profile. Transient nausea and hypoglycaemia were the most commonly reported adverse events. Other less frequent side effects are redness, swelling, bruising, or itching at the site of Pramlintide injection, loss of appetite, pain in abdomen, indigestion, excessive, cough, sore throat, tiredness, dizziness, joint pain. As there is risk of hypoglycaemia, dose of insulin should be decreased by 50% and blood glucose levels should be monitored closely at the start of therapy.[34]

DUAL PPAR AGONIST

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily with potential pharmacologic targets for combating obesity and diabetes.[35] PPARs play a central role in insulin sensitivity, lipid metabolism, and inflammation. PPAR family consists of three isoforms i.e. PPAR-α, PPAR-β and PPAR-Y, each having peculiar tissue distribution pattern. Drugs activating PPAR-α, produces significant improvements in deranged lipid profile and decrease atherosclerotic lesions, without any effect on plasma glucose levels. PPAR-γ appears to improve glycaemic control by increasing peripheral insulin sensitivity and reducing hepatic gluconeogenesis, thereby preserving the beta-cell function.[36] Hence there is a resurgence of interest in the development of new antidiabetic drugs which combine the insulin-sensitizing effects of PPAR-γ activation with the additional lipid-modifying activity of the PPAR-α. Glitazars are a new generation of dual PPAR α / Y agonists. Dual activation of PPAR Y and PPAR α enhances the action of adiponectin and increases the expression of its receptor in white adipose tissue.[35]

Muraglitazar

Muraglitazar is an oxybenzylglycine dual PPAR α/γ agonist that is in advanced clinical development for the treatment of type 2 diabetes associated dyslipidemia.[37] Administration of Muraglitazar in T2DM patients improved glycaemic control associated with decreases in HbA1c, fasting plasma glucose, insulin and FA levels while increasing insulin sensitivity. In addition, Muraglitazar improved TG, HDL-C, Apo B and non-HDL-C levels.[35] Furthermore, when given in combination with the insulin secretagogue glyburide in patients failing on monotherapy, Muraglitazar provided more effective glycaemic control than in the control group. Finally, administration of Muraglitazar (5 mg/day) resulted in a greater improvement in HbA1c and further improvement in the lipid profile than pioglitazone (30 mg/day) in patients on metformin. Like PPAR γ agonists, Muraglitazar increases body weight as well as edema,

limiting its clinical dose to 5 mg/day, a dose at which the drug likely activates PPAR-γ predominantly.[35] Studies have suggested that Muraglitazar at the dose of 5 mg/day, increased the incidence of adverse cardiovascular events such as myocardial infarction, stroke, transient ischemic attack, and congestive heart failure compared with placebo or pioglitazone. Hence its development was discontinued in 2006.[36]

Tesaglitazar

Tesaglitazar, another drug from the same class, was initially studied in non-diabetic individuals with metabolic syndrome and showed a substantive improvement in the lipid profile. The biologically active form of tesaglitazar is the (S)-enantiomer, whereas, the (R)-enantiomer is approximately 100 times less potent than its antipode.[37] After a single oral or intravenous dose of 1 mg of tesaglitazar, the maximum plasma concentration was achieved at the end of 1 hour with 100% bioavailability. Tesaglitazar was well tolerated with high (99.9) plasma protein binding of tesaglitazar.[37] However, concerns raised in various phase III clinical trials, regarding elevated serum creatinine and associated reduction in glomerular filtration rate, were sufficient to deter further development.

Aleglitazar

Aleglitazar is a newer member belonging to the family of glitazar. It has successfully completed Phase II clinical trials and currently is in Phase III clinical trials.[38] Preliminary evidence from clinical studies with Aleglitazar is promising, with reported improvements in glycaemia, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, apolipoprotein B and blood pressure. However, PPAR-α- and -γ-associated side effects have been observed and additional large-scale, long-term clinical studies are necessary to better understand the clinical implications of these effects.

Various glitazars were streamlined for the treatment of type 2 DM but many got disqualified due to their adverse effects which caused more harm than gain. Thus the development of Navaglitazar, Ragaglitazar, Farglitazar which were promising initially, were discontinued.[39] However, the clinical safety and efficacy of Aleglitazar is currently under Phase III clinical investigation for reduction of cardiovascular events in patients with type II diabetes and recent acute coronary syndrome.[40] Hopefully this drug will surpass its predecessor in terms of safety, efficacy and adverse effect profile.

BROMOCRIPTINE

Bromocriptine is a centrally acting dopamine D2 receptor agonist approved by the US FDA in May 2012 as an adjunct to diet and exercise to maintain euglycemia in patients with type 2 DM.[41] The rationale behind using bromocriptine for the treatment of type 2 DM is derived from the study of metabolism in migrating birds who develop seasonal insulin resistance and dopamine plays a key role in it. Dopamine is known to be the most abundant adrenergic neurotransmitter in the central nervous system. Adrenergic nervous system plays an important role in regulation of glucose levels. Also in preclinical studies it was observed that decreased hypothalamic dopaminergic tone plays a role in the pathogenesis of insulin resistance. Therefore a dopamine modulator may prove beneficial in modifying the autonomic responses and ensuring euglycemia.[41]

Bromocriptine is the first drug for treatment of diabetes to be approved under the FDA's new guidelines which require clinical trials to demonstrate no increased cardiovascular risk. The recommended initial dose is 0.8 mg daily, escalated by 0.8 mg weekly until the target range (1.6 - 4.8 mg) or till maximal tolerance is reached.[41] It should be administered as a single daily dose within two hours of waking in the morning and preferably with food to minimize nausea. The most common side effects associated with bromocriptine mesylate are nausea, fatigue, dizziness, vomiting and headache.

It can be used as monotherapy or as adjunctive therapy to currently available antidiabetic medications like metformin/sulfonylurea. Its use is however, not recommended for the treatment of type-1 diabetes or diabetic ketoacidosis. There is paucity of data in regards to its efficacy when used in combination with either insulin or thiazolidinediones.

The complete review of these newer anti-diabetic drugs has been summarised in table 2.

SUMMARY

There have been tremendous advancements in the management of type II DM in the past few years. The decision regarding the choice of anti-diabetic medications always places the practitioners at crossroads. The promising newer anti-diabetic medications further add to the dilemma. These newer agents are frequently used in combinations to the currently used oral anti-diabetic drugs. The treatment of DM is always tailored to the individual patient, depending upon the diabetic profile and other associated co-morbid conditions. The need of further studies for evaluating the risk benefit and cost benefit analysis of these newer drugs cannot be overemphasized.

Funding: No funding sources
Competing interests: There are no competing interests to declare

Table 2: Newer anti-diabetic drugs.

Class	Agents	Mechanism of Action	Adverse effects	Current Status
Glucagon Like Peptide-1 mimetic	Exenatide Liraglutide	They stimulate insulin secretion and decreases hepatic glucose production by modulating incretin system	Hypoglycaemia	Approved
Dipeptidyl Peptidase-IV Inhibitor	Sitagliptin Vildagliptin* Saxagliptin	Inhibits DPP-IV mediated degradation of GLP-I & GIP, which leads to increased insulin secretion and decreased hepatic glucose production	Nasopharyngitis, Headache, Arthralgia, Upper Respiratory tract infections	Approved
Sodium Glucose Transport Protein Inhibitor	Canagliflozin, Dapagliflozin, Remogliflozin, Sergliflozin	They inhibit glucose reabsorption from kidney thus lowering blood glucose concentration	Urinary tract infections	Dapagliflozin is in Phase III, while Remogliflozin, Sergliflozin are withheld in Phase II
Amylin Mimetics	Pramlintide	By mimicking Amylin action they suppress glucagon secretion and attenuate hepatic glucose production	Loss of appetite, pain in abdomen, Indigestion, Dizziness	Approved
Dual PPAR ۲ agonist	Aleglitazar, Muraglitazar, Ragaglitazar, Naveglitazar	They improve insulin sensitivity, reduce atherogenic triglycerides and raises cardio -protective HDL levels	Cardiovascular events such as myocardial infarction, stroke, transient ischemic attack, and congestive heart failure	Trials withheld except for Aleglitazar which is in Phase III
Dopamine agonist	Bromocriptine	They modify autonomic responses maintaining euglycemia	Hallucinations	Approved
*Approved by the European Union but not by the US FDA yet.				

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doi: 10.5455/2319-2003.ijbcp20130102
Cite this article as: Deshmukh VS, Motghare VM, Padwal SL, Jaykare S, Patil J, Pise H. Newer drugs in the management of diabetes mellitus. Int J Basic Clin Pharmacol 2013;2:4-11.