Drugs In Pipeline For Type-2 Diabetes
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Citation

Abstract
Hyperglycemia, obesity, insulin resistance, dyslipidemia and hypertension are interrelated cardiometabolic risk factors for the development of type-2 diabetes and metabolic syndrome. Prevalence of type-2 diabetes is growing at an alarming rate. Treatment target for type-2 diabetes is to keep daily glucose profile as close as possible to that of a non-diabetic person. Sulfonylureas, thiazolidinediones, meglitinides, biguanides and acarbose inhibitors are already being used in controlling glucose levels in type-2 diabetes. This review discusses the new drugs with novel mechanism of actions; which are in pipeline and were marketed recently or will be in market in near future.

INTRODUCTION
Type-2 diabetes is the most common metabolic disorder worldwide, and its prevalence is growing at an alarming rate in both developed and developing countries. This growth has been related to the increased prevalence of obesity. A cluster of interrelated cardiometabolic risk factors is closely related to the development of type-2 diabetes and cardiovascular disease. Obesity, hyperglycemia and insulin resistance, dyslipidemia, inflammation, and hypertension represent interrelated therapeutic targets in the battle against the increasing prevalence of type-2 diabetes. The evidence, that obesity and diabetes is associated with risk of carcinoma has made the picture murkier. The most common type of diabetes mellitus, type-2, seems to be associated with liver and pancreas cancer and probably with colorectal cancer. The health consequences and economic costs of the overweight, obesity and type-2 diabetes epidemics are enormous.

Treatment targets for type-2 diabetes include restoring blood glucose to normal levels so as to abolish diabetic symptoms; and the risk of acute and chronic metabolic complications. In a large scale study, a 1% reduction in HbA1c resulted in 21% reduction in diabetic related deaths, 37% reduction in microvascular disease, 14% reduction in myocardial infarction and 21% reduction in all diabetes related end points.

Oral antidiabetic agents for type-2 diabetes already available in market include sulfonylureas (tolbutamide, chlorpropamide, glibenclamide, gliclazide, glipizide, glimepiride); biguanides (phenformin, metformin); thiazolidinediones (pioglitazone, rosiglitazone) meglitinides (repaglinide, nateglinide); alpha-glucosidase inhibitors (acarbose, miglitol, voglibose) and miscellaneous ones (aspartame, chromium picolinate, guar gum, glucomannan), available either singly or as combinations. With all these available options, still, sometimes glucose control is not maintained; and many patients ultimately have to put on insulin therapy. To fill the vacant space and to satisfy the ever growing human-urge of research, new compounds have surfaced which may stake its claim in the market in near future.

NEW ANTIDIABETIC DRUGS IN THE PIPELINE
Many new antidiabetic drugs with novel mechanism of actions are in the pipeline; they have either been introduced recently or are undergoing late phase 3 trials or an NDA has been applied for. These drugs with their classes are:

- Dopamine-2 (D2) receptor agonist: Bromocriptine mesylate
- Glucagon-like Peptide-1 (GLP-1) analogues: Exenatide, Liraglutide, Albiglutide
- Dipeptidyl Peptidase-4 (DPP-4) inhibitors: Alogliptin, Linagliptin, Saxagliptin, Vildagliptin
- Dual Peroxisome Proliferator-Activated Receptor (PPAR) agonists: Aleglitazar, Muraglitazar, Tesaglitazar
- Sodium-Glucose Transport Proteins-2 (SGLT-2) inhibitors: Dapagliflozin, Remogliflozin, Sergliflozin
DOPAMINE-2 RECEPTOR AGONIST: BROMOCRIPTINE MESYLATE

Idea of use of Bromocriptine in type 2 diabetes (used otherwise in parkinsonism disease) originated by studying the metabolism of migrating birds; that they develop seasonal insulin resistance, and this insulin resistance if occurred in humans lead to type 2 diabetes, and dopamine is responsible for it.[12] On May 5th, 2009, FDA approved bromocriptine mesylate (cycloset) 0.8-mg quick-release tablets for use alone or with other antidiabetic agents in the management of type 2 diabetes. The recommended starting dose is 0.8 mg taken once daily within 2 hours of waking and is titrated in increments of 0.8 mg/week to a target dose ranging from 1.6 to 4.8 mg. Bromocriptine, a centrally-acting dopamine D₂ receptor agonist, when administered as a single timed morning dose, is thought to act on circadian neuronal activities within the hypothalamus to reset abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in insulin-resistant patients.[5] This is the 1st chronotherapeutic based treatment for type 2 diabetes.

Adverse events most commonly reported in clinical trials of bromocriptine included nausea, fatigue, vomiting, headache, and dizziness. These events lasted a median of 14 days and were more likely to occur during initial titration of the drug. None of the reports of nausea or vomiting were described as serious. The FDA warns that bromocriptine can cause orthostatic hypotension and syncope, particularly on initiation of therapy and dose escalation.[5]

GLP-1 ANALOGUES

GLP-1 analogues have been developed by observing that glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1); also known as incretins, are released from upper and lower bowel that augments glucose-dependent insulin secretion. This action is seen more with GLP-1. GLP-1 also reduces glucagon secretion, slows gastric emptying and decreases appetite; so ultimately reduces postprandial glucose rise and weight loss.[13]

Exenatide is a 39-amino acid peptide, a GLP-1 analogue and insulin secretagogue with glucoregulatory effects. Exenatide is indicated for type 2 diabetic patients whose diabetes is not well-controlled by other oral medications. Exenatide is administered as a subcutaneous injection (under the skin) of the abdomen, thigh, or arm, 30 to 60 minutes before the first and last meal of the day. Exenatide enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.[14]

The medicine is available in two doses: 5 mcg and 10 mcg. Treatment often begins with the 5 mcg dosage, which is increased if adverse effects are not significant. The main side effects of exenatide use are gastrointestinal in nature, including acid or sour stomach, belching, diarrhea, heartburn, indigestion, nausea, and vomiting; exenatide is therefore not meant for people with severe gastrointestinal disease. Other side effects include dizziness, headache, and feeling jittery. Few cases of pancreatitis were reported, so FDA has issued a statutory warning.[14]

In an open label randomized controlled trial of 551 patients, exenatide treatment for 26 weeks was associated with 2.3 kg weight loss; however, gastrointestinal symptoms were more common in the exenatide group, including nausea (57.1%), vomiting (17.4%) and diarrhea (8.5%). For most patients, the nausea is mild to moderate and goes away entirely after a few days or weeks.[15]

It is evident that one obvious advantage with exenatide is weight loss during treatment, which is seen only with other two antidiabetic drugs i.e. metformin and acarbose, but one obvious disadvantage is that it has to be injected.

Liraglutide is long acting GLP-1 analogue that awaits FDA and EMEA (European Medical Agency) approval to be used in type 2 diabetes as once daily subcutaneous injection,[16] but as on April 2, 2009 FDA advisory panel has expressed serious concern that the drug causes thyroid tumors. Otherwise in a randomized study, in subjects with type 2 diabetes, once-daily liraglutide induced similar glycemic control, reduced body weight, and lowered the occurrence of hypoglycemia compared with glimepiride, when both had background therapy of metformin.[17]

Albiglutide, another GLP-1 analogue is a novel dipeptidyl peptidase-4-resistant (Dipeptidyl peptidase-4 causes metabolism of GLP-1 and its analogues) glucagon-like peptide-1 dimer fused to human albumin designed to have sustained efficacy in type 2 diabetics. It is still under investigation. Its half life ranges from 6-7 days, so weekly injections can be given.[7]

DPP IV INHIBITORS

Dipeptidyl peptidase IV (DPP IV) is the major enzyme responsible for degrading the incretins in vivo. So the
blockade of incretin degradation increases their physiological actions, including the stimulation of insulin secretion and inhibition of gastric emptying. Incretins (GIP & GLP-1) have powerful effects on beta-cell differentiation, mitogenesis and survival. By potentiating these pleiotropic actions of the incretins, DPP IV inhibition can therefore preserve beta-cell mass and improve secretory function in diabetics. (18)

The first agent of this class, sitagliptin, (marketed under trade name Januvia) was approved by the FDA in October 2006, for use in addition to diet and exercise to improve blood sugar levels in patients with type 2 diabetes, alone or in combination with two other commonly prescribed oral diabetes medications, metformin or a PPAR-agonist, when either of these drugs alone, along with diet and exercise, don't provide adequate blood sugar control. Januvia was examined in a total of 2,719 patients with type 2 diabetes. These studies demonstrated improved blood sugar control when Januvia was used alone or in patients not satisfactorily managed with metformin or a PPAR agonist. The most common side effects in clinical studies were upper respiratory tract infection, sore throat, and diarrhea. (19)

Vildagliptin (trade name Galvus) is another oral antidiabetic drug which is a DPP-IV inhibitor. The Food and Drug Administration had demanded additional clinical data before it could approve vildagliptin. While the drug is still not approved for use in the US, it has been approved by EMEA for use within the EU. (20)

Other drugs in this class are saxagliptin, linagliptin and alogliptin, which are under development. Takeda has submitted a New Drug Application (NDA) for alogliptin to the FDA, after positive results from Phase III clinical studies. (21) Similarly, AstraZeneca has submitted NDA for saxagliptin under trade name Onglyza to FDA and EMEA for approval. (22)

### DUAL PPAR AGONISTS

Fibrates, the PPAR alpha agonists, first used in the 1970s, lower plasma triglycerides and VLDL particles and increase HDL cholesterol; effects that are associated with cardiovascular benefit. PPAR gamma agonists like thiazolidinediones, influence free fatty acid flux and thus reduce insulin resistance and blood glucose levels. PPAR gamma agonists are therefore used to treat type-2 diabetes. PPAR alpha and gamma agonists also affect inflammation, vascular function, and vascular remodeling. (23) Several basic and clinical studies have exemplified the beneficial effects of PPAR alpha and PPAR gamma ligands in preventing the cardiovascular risks. The PPAR alpha/gamma dual agonists are developed to increase insulin sensitivity and simultaneously prevent diabetic cardiovascular complications. Such compounds are under clinical trials and proposed for treatment of Type-2 diabetes with secondary cardiovascular complications. (10)

However, PPAR alpha/gamma dual agonists such as muraquitazar, tesaglitazar and ragaglitazar have been noted to produce several cardiovascular risks and carcinogenicity, which raised number of questions about the clinical applications of dual agonists in diabetes and its associated complications. Further studies are on the track to develop PPAR alpha/delta and PPAR gamma/delta dual agonists and PPAR alpha/gamma/delta pan agonists for the treatment of diabetic cardiovascular complications. (10)

### SODIUM-GLUCOSE TRANSPORT PROTEINS-2 (SGLT-2) INHIBITORS

Sodium-dependent glucose co-transporters are a family of glucose transporters found in the intestinal mucosa of the small intestine (SGLT1) and the proximal tubules of the nephrons (SGLT2 and SGLT1). They contribute to renal glucose reabsorption. SGLT1 is responsible for only 2% renal glucose reabsorption, while SGLT2 is responsible for 98% of renal glucose reabsorption. (24)

SGLT2 has a 1:1 ratio of sodium-glucose transport. SGLT1 works similarly but has a 2:1 ratio of sodium-glucose transport. SGLT2 inhibitors are being developed as potential antidiabetic agents because of their ability to specifically reduce transcellular epithelial glucose reabsorption. (25)

Dapagliflozin, the most advanced compound in this novel class of oral antidiabetic agents, is currently in phase III clinical testing for the treatment of type 2 diabetes. The drug was discovered by Bristol-Myers Squibb and has been licensed to AstraZeneca for development and commercialization. Two trials are currently recruiting participants: one in diabetic subjects not adequately controlled on metformin alone and the other in those not adequately controlled with diet and exercise alone. (25)

Another drug of this class, Remogliflozin etabonate is a prodrug based on benzylpyrazole glucoside and is metabolized to its active form, remogliflozin, in the body. It is a potent and highly selective SGLT2. Orally administered remogliflozin etabonate increased urinary glucose excretion in a dose-dependent manner in both mice and rats. (26)
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drug is being developed by GlaxoSmithKline.

Sergliflozin etabonate is a benzylphenol glucoside based prodrug, which is again a potent SGLT2 inhibitor and is currently under investigational phase. (27)

CURRENT POSITION

Many of these drugs have been approved like bromocriptine mesylate, exenatide, sitagliptin, vildagliptin (only in EU); while questions have been raised on the safety issue regarding many new compounds being developed to counter type 2 diabetes and FDA has asked for additional clinical trial data. Never the less, these agents provide novel therapeutic mechanisms for controlling type 2 diabetes. So, let’s keep our fingers crossed!!

References

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