



DIABETES MELLITUS TYPE II: REVIEW OF ORAL TREATMENT OPTIONS

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ABSTRACT

Introduction: Type 2 diabetes is a chronic disease that has very serious complications if not appropriately treated. Many oral hypoglycemic agents have been effective recommendations in treating type 2 diabetes. Sitagliptin (Januvia), Exenatide (Byetta), and Exubera are 2 newer agents that have proven efficacious in disease management. The purpose of this paper is to review the efficacy, use, and tolerability of oral hypoglycemic agents that are older compared to Sitagliptin (Januvia), Exubera, and Exenatide (Byetta).

Treatment Options: Oral hypoglycemic agents for treatment of type 2 diabetes comprise of seven different classes. Each one of those classes has its advantages and disadvantages. Sulfonylureas, Short-acting insulin Secretagogues, Biguanides, alpha-Glucosidase inhibitors, and Thiazolidinediones are the older classes. Sitagliptin (Januvia) is a dipeptidyl-peptidase-4 inhibitor (DPP-4), and Exenatide is an incretin mimetic which inhibits the enzymatic activity of DPP-4. Exubera is an inhaled newly approved interesting technique in treatment of type 2 diabetes. Oral combinations have improved patients' compliance and had supportive data in mastering disease management.

Discussion: Selection of an appropriate pharmacological agent is based on considerations of its clinical efficacy as far as the risk versus benefit, cost, characteristics of the patient, and levels of glucose control. Sulfonylureas are best for patients with diagnosis of type 2 diabetes when they are less than 40 years of age. Short-acting insulin secretagogues have a rapid onset of action. Metformin is an appropriate agent to reduce weight and decrease insulin resistance. Thiazolidinediones are very important in maintaining glycemic control and improve beta cell function. They have enormous evidence of reducing HbA1C and Blood glucose levels. Sitagliptin and Exenatide are new innovations proven to improve glycemic control as well as inhaled Exubera therapy.

Conclusion: Sitagliptin, Exenatide, and Exubera do offer a new approach in assisting patients with type 2 diabetes. Benefits of pharmacological agents are not complete unless accompanied by non-pharmacological treatments.

Keywords: Type 2 diabetes, Sulfonylureas, Thiazolidinediones, alpha-glycosidase inhibitors, Biguanides, Sitagliptin, Exenatide, Exubera, short-acting insulin secretagogues.

INTRODUCTION

Twenty one million people in the United States, accounting for 7 % of the population, have diabetes mellitus (DM) according to the American Diabetes Association (ADA). One third of these people are not aware that they are diabetic as another 41 million people are pre-diabetic. The total economic cost annually of diabetes in year 2002 was approximately 132 billion dollars. Diabetes is more frequent among African Americans, Hispanic Americans, American Indians, and Asian/ Pacific Islanders. In people age 20 and older 9.6% have diabetes, and in patients 60 years or older 20.9 % have diabetes. The most common complications of Diabetes are cardiovascular disease and stroke.²⁴ Diabetes is the sixth leading cause of death in the U.S, according to the center for disease control and prevention (CDC). This accounts to 224,000 deaths in year 2002 only.

Oral hypoglycemic agents and lifestyle modifications such as diet and physical activity are the mainstay of therapy in patients with type 2 diabetes. The

algorithm, Figure 1, can help identify and treat patients with type 2 diabetes. Further health issues need to be addressed such as foot care, peripheral diabetic neuropathy, as well as nephropathy and retinopathy monitoring. Many oral hypoglycemic agents exist that have proven to be successful in lowering significant parameters in disease monitoring such as HbA1C lowering, fasting blood glucose reduction and peak postprandial plasma glucose.¹

Currently, many oral hypoglycemic agents are FDA approved and have shown to be very effective in type 2 diabetes. Certified diabetes educators and other clinical pharmacists played an important role in diabetes education, assisting in preventing complications of this chronic disease. Nine different agents have shown to be very efficacious in treating type 2 diabetes; seven are oral ,one is an inhaled product and one is injectable. One of the therapies recently approved in 2006 belongs to a category of dipeptidyl peptidase-4 enzyme (DPP-4) inhibitor called Sitagliptin (Januvia). Exenatide (Byetta) is also a

new incretin-based injection therapy known as incretin mimetic approved by the FDA in 2005. Another approved treatment in 2006, is an inhalation powder called Exubera which is first inhaled product used for diabetes.

Several combination products have shown to be effective in treatment of type 2 diabetes. Several factors are of importance in choosing the best agent, such as tolerability, effectiveness, contraindicating disease, and side effects profile. Also patient cofactors play an additional important role. The main purpose of this paper is to review different oral hypoglycemic agents, their use, and effectiveness and compare them to the new approved therapies: sitagliptin (Januvia), exenatide (Byetta), and the new inhalation technology in diabetes management Exubera.

TREATMENT OPTIONS

Sulfonylureas

This class of drugs had been introduced in the 1950's and has played an important role in the management of type 2 diabetes since its introduction to the market. They work by binding to sulfonylurea receptor (SUR) on beta cells of the pancreas thus enhancing insulin secretion from the pancreas blocking hepatic glucose production when being transported through the portal vein. Sulfonylureas are divided into first and second generation agents. First generation which are less potent include: Acetohexamide (dymelor), Chlorpromazine (Diabinese), Tolazamide (Tolinase), and Tolbutamide (Orinase). Second generation include: Glipizide (Glucotrol, Glucotrol XL), Glyburide (Diabeta, Micronase), and Glimepiride (Amaryl).

These agents are metabolized by the liver by CYP 450 enzymes (CYP 2C9) with renally eliminated active metabolites needed dosing adjustment in patients with renal failure. The half-life of metabolites is directly related to the risk of hypoglycemia. Chlorpropamide and Glyburide have highest risk of hypoglycemia, and long duration of effect of the former is problematic in old people with renal failure. Advantages of these agents according to studies include a decrease of HbA1C by 1.5% to 2% as well as fasting plasma reductions of 60-70 mg/dl.^{1,2,5} Also they are the least expensive and most of them have generic availability. Some disadvantages include weight gain (4-6 kg), hypoglycemia and a primary failure rate of 10 to 15 %. Also they have no effect on triglycerides or total cholesterol. Some of the side effects include hyponatremia, syndrome of inappropriate antidiuretic hormone (SIADH) especially with first generation agents. Patients with higher response to sulfonylureas are those who are diagnosed with type 2 diabetes before age 40, level of fasting blood glucose of less than 300 mg/dl, and patients with disease duration of less than 5 years before drug therapy is started.

In a recent study by Bolen S, et al the authors

summarized the literature on the benefits and harms of new and older agents (sulfonylureas, metformin, and others) in the treatment of type 2 diabetes. Original articles and systematic reviews were searched from the Medline, Embase and Cochrane center register of controlled trials databases. There were 216 cohort and controlled trials studies, and two systematic reviews addressing the benefits and harms of available oral diabetic drugs in the USA. The studies with intermediate endpoints were reviewed only excluding the ones with major end points (cardiovascular mortality). Thiazolidinediones increased HDL levels from 0.08 to 0.13 mmol/L and LDL levels of 10 mg/dl compared with other agents. Metformin was the only agent that had decreased LDL and had no effect on body weight. Greater hypoglycemia was seen with sulfonylureas and repaglinide. The study showed that older and less expensive agents (sulfonylureas and metformin) have similar or even superior effects on lipids, glycemic control (HbA1C decrease by 1%), and other intermediate end points when compared with alpha-glucosidase inhibitors, meglitinides, and thiazolidinediones.²

Short acting insulin secretagogues known as Metiglinides

Nateglinide (Starlix) and Repaglinide (Prandin) are the two Metaglinides approved in the U.S. They both stimulate the secretion of insulin from the pancreatic beta cells similarly to sulfonylureas. These two agents are though rapid-acting and have a short half-life of 1 to 1.5 hours. They are mainly metabolized by CYP 2C9 and CYP3A4. When used alone they reduce postprandial glucose levels and HbA1C levels. They should be dosed half an hour prior to each meal and one of the advantages is that they can be used in renal insufficiency. Another advantage is their use as alternative in hypoglycemic patients with low-dose sulfonylureas. Due to the glucose sensitive release of insulin they cause less hypoglycemia in comparison with sulfonylureas. One of the side effects is an increase in body weight with no effect on cholesterol. In six month trials, both agents reduced fasting plasma glucose and HbA1C by 31mg/dl and 0.6 % for repaglinide and 13 mg/dl and 0.4% for nateglinide.^{8,9}

Carroll MF et al, compared the efficacy of acute premeal administration of glipizide versus nateglinide in control of postprandial hyperglycemia in patients with type 2 diabetes. The subjects included in this study were 10 females and 10 males that were randomly administered 10 mg glipizide 30 minutes pre-meal, 120 mg nateglinide 15 minutes pre-meal, 10 mg glipizide plus nateglinide 30 and 15 minutes pre-meal, or placebo pills 30 and 15 minutes pre-meal in a double-blind fashion. Analysis of glucose and insulin was done through drawing of blood at different hours

in relation to the meal (-0.5, 0, 0.5, up to 4 hours after the meal). The peak levels of glucose after meals was higher with placebo than nateglinide (6.1 versus 4.2), glipizide (6.1 versus 4.3) and glipizide plus nateglinide (6.1 versus 4.1). Nateglinide and glipizide are equally effective when it comes to control of post-meal hyperglycemia when administered acutely before meals. The only thing is that insulin response after meals is higher with glipizide. Choosing one of those agents (glipizide vs. nateglinide) must be determined by factors different than controlling postprandial hyperglycemia.³

Biguanides

Glucophage, Glucophage XR (metformin) is the only biguanide approved in the U.S. Mechanism of action is through reducing glucose production by the liver, reducing absorption of glucose, and enhancing uptake of glucose into skeletal muscle. Glucophage is not extensively metabolized and it is eliminated by renal tubular secretion and glomerular filtration. Its half-life is six hours, and its effect lasts about 24 hours.⁷ Scherthaner G, et al compared the efficacy and safety of glucophage to another Thiazolidinedione (pioglitazone). The study duration was 52 weeks including a number of 1199 patients with poorly controlled type 2 diabetes (HbA1C: 7.5-11%) who randomly received either metformin 850 mg three times daily or pioglitazone 45 mg daily. The results did show a mean decrease of HbA1C of 1.5 %, a decrease of fasting plasma glucose by 39.6 mg/dl, a reduction in the total cholesterol to HDL ratios, and a 2.5 kg decrease in weight in the Glucophage (metformin) group. The total cholesterol to High density lipoprotein cholesterol ratios decreased in a similar way with both treatments. Urinary albumin to creatinine ratio decreased by 19% with pioglitazone but remained unchanged with glucophage use.¹²

An advantage of this class of drugs is that it works best when fasting blood glucose levels are above 300, and when sulfonylureas do not have the ability to stimulate release of insulin from beta cells at high levels of glucose. Also it is the only class proven to decrease risk of mortality and cardiovascular death.²⁰ Some disadvantages of this class is it cannot be given in patients with renal insufficiency. Some of the adverse effects include GI side effects of diarrhea (30%) diminished by taking Glucophage XR. It also has the potential of causing lactic acidosis in rare cases. The dose of metformin is influenced by the presence of risk factors for lactic acidosis. To mention that if a patient is going to undergo a certain procedure that uses contrast dye medium (CT scan, angiography, etc...), metformin should be stopped the day of the procedure or sooner and not restarted until two days of the procedure after making sure that kidneys are functioning properly. This intervention will decrease the chance of lactic acidosis occurrence.

In march of 2004, Merck announced the approval of metformin as a first oral anti-diabetic agent to be used in children above ten years of age in Europe (including all seventeen European countries). Treatment was initiated using a dose of 500 mg daily and can be increased up to a maximum dose of 2000 mg per day to achieve adequate glucose control.

Thiazolidinediones (TZDs)

Pioglitazone (Actos) and Rosiglitazone (Avandia) are the two FDA approved TZDs for Type 2 diabetes. They act by binding to the Peroxisome Proliferative insulin activated receptors enhancing Sensitizing effects of insulin at liver, muscle as well as fat tissues also by inhibiting glucose formation by liver. This class of drugs has shown to be metabolized in the liver through CYP 450 isoenzymes 2C8 (Pioglitazone, rosiglitazone), 3A4 (pioglitazone), and 2C9 (rosiglitazone).

Chilcott et al, published a systemic review study in 2001, measuring the clinical effectiveness of pioglitazone in treating type 2 diabetes as monotherapy and in combination with other anti-diabetic drugs. The results of the study showed that in both combination and immunotherapy pioglitazone caused a decrease in glucose levels in the blood up to 95 mg/dl and a decrease in HbA1C of up to 2.6%. At doses of more or equal to 30 mg/day pioglitazone was associated with a decrease in triglycerides levels (-30 - 70 mg/dl) and an increase in high-density lipoprotein (HDL) levels (-4-5mg/dl). Disadvantages of the drug included weight gain up to 4 kg over 16 weeks. Some of the adverse of pioglitazone in the study included mild edema in up to 11.7 % of patients. As a conclusion of the study, the best role of pioglitazone is an additive therapy to metformin or sulfonylurea patients whose condition is not well managed with monotherapy and in whom a metformin-sulfonylurea combination is contraindicated.¹³

With this class of agents, maximum glycemic lowering effect occurs in 3 to 4 months of therapy. Adverse effects associated with this class are hepatotoxicity with both drugs thus it is contraindicated in patients where ALT levels are 2.5 times the upper limit of normal. Another adverse effect is fluid retention making TZDs contraindicated in patients with class III, IV Heart Failure. Rosiglitazone according to a recent article in NEJM was found to be associated with a significant increase in the risk of myocardial infarction and death from cardiovascular causes. Based on the latest update from the JAMA, rosiglitazone increased the risk of MI and CHF, but was not associated with an increased risk of cardiovascular mortality. Pioglitazone appears to be safer when compared to rosiglitazone since new data showed no increase in mortality or total cardiovascular events when treating type 2 diabetes. The FDA recently decided to make an addition to the pioglitazone label making it the only

TZD with safety data from the cardiovascular outcomes trial. These drugs are also considered pregnancy category C.

Alpha-Glucosidase inhibitors

Acarbose (Precose) and miglitol (Glyset) were approved in mid 1999 in the U.S. They competitively inhibit alpha-glucosidase enzymes in the small intestine which delays the breakdown of complex carbohydrates and sucrose thus decreasing postprandial glucose increase. Postprandial glucose concentrations were diminished (40 to 50 mg/dl) without affecting much of the Fasting blood glucose nor the HbA1C levels with the use of both agents according to studies.¹⁴

The main advantages of the use of these agents are targeting patients with high postprandial blood glucose with almost normal values of HbA1C and fasting blood glucose and minimal effect on body weight. Some of the disadvantages include minimal effect on cholesterol, and possible elevations in liver function tests with acarbose requiring frequent monitoring of hepatic enzymes. Miglitol which is excreted by kidneys should be used with caution in renal failure patients. Adverse effects associated with these agents are GI effects such as flatulence, bloating, abdominal discomfort, and diarrhea. Both agents ought to be taken with the first bite of the meal because of the mechanism of inhibiting enzyme activity.

Combination products

The use of combination therapies improved patient's compliance to the use of the oral diabetic agents. Glucovance is an example of a combination of glyburide and metformin. This combination was proven to reduce fasting plasma glucose by 50 to 60 mg/dl and HbA1C by 1.7 % to 1.9 %. This effect was greater than that of each agent as Monotherapy. Other combinations include glipizide/metformin (Metaglip), rosiglitazone/metformin (Avandamet), pioglitazone/glimepiride (Duetact).^{9,10,11}

Smilev D et al, published a study in 2007 showing the effect of combination of metformin/rosiglitazone approved in October 2002 by the FDA in type 2 diabetes. The results were that the combination improved insulin sensitivity in a complimentary fashion; metformin decreases glucose production by liver and TZDs increase skeletal muscle use of glucose which showed very beneficial in treating diabetes type 2.²⁶

Dipeptidyl peptidase-4 Inhibitor (DPP-4 Inhibitor)

The first FDA approved DPP-4 Inhibitor in October 2006 in the United States is Sitagliptin (Januvia). Incretin hormones released in the intestine in response to meals play a role in regulation of glucose homeostasis. These hormones are deactivated by DPP-

4 enzymes. Sitagliptin inhibits the inactivation of incretin hormones by inhibiting the DPP-4 enzyme increasing incretin levels. This process leads to an increase in the release of insulin and a decrease in the levels of glucagon in the blood. Raz I, Hanefeld M, et al. conducted a study to measure the efficacy and safety of Sitagliptin as monotherapy in patients with type 2 diabetes and HbA1C of more or equal to 7 % and less or equal to 10% on exercise and diet for 18 weeks. There were 521 patients aged 27-76 years of age randomized to treatment with Sitagliptin 100 mg daily, 200 mg daily, or placebo. After 18 weeks of therapy, HbA1C and fasting plasma glucose was reduced significantly with both 100, 200 mg doses when compared to placebo. Markers of insulin secretion, Beta cell function and insulin ratio were dramatically improved by Sitagliptin.¹⁵

Another study by Hermansen K, et al. which included patients with type 2 diabetes poorly controlled on glimepiride (Amaryl) alone or on glimepiride and metformin for 24 weeks treatment period. 441 patients received addition of sitagliptin 100 mg daily or placebo. There were 212 patients on glimepiride and 229 patients who received glimepiride plus metformin. Primary efficacy endpoints were a change in HbA1C from baseline to week 24. Secondary efficacy endpoints were fasting plasma glucose, 2 hour post-meal glucose, as well as lipid measurements. After 24 weeks, Sitagliptin reduced HbA1C by 0.74% relative to placebo. In the subset of patients on glimepiride plus metformin, sitagliptin reduced HbA1C by 0.89% relative to placebo compared with 0.57% reduction in patients on glimepiride alone. Addition of Sitagliptin reduced fasting plasma glucose by 20.1 mg/dl and increased beta cell function by 12 % relative to placebo (p<0.05). Sitagliptin decreased 2 hours post-prandial glucose by 36.1 mg/dl relative to placebo. Addition of sitagliptin was well tolerated with a relative high risk of hypoglycemia.¹⁶

Adverse events associated with the use of Januvia (Sitagliptin) include upper respiratory tract infections and headache. Many data show that an advantage to Sitagliptin is a favorable safety profile when compared to other oral diabetic treatments. Lack of adverse reactions with this drug including neutral effect on weight, no hypoglycemia, as well as absence of drug interactions makes it a very beneficial oral therapy.^{17,18}

Vildagliptin (Galvus, Novartis) is a new DPP-4 taken once daily that has been approved in Europe, Iceland and Norway. It is approved for the use along with sulfonylureas, thiazolidinediones, and metformin.²⁷ This medication has been shown to lower blood sugar levels, without causing weight gain or high incidence of hypoglycemia that is usually caused by other TZDs

and sulfonylureas.²⁸ No major side effects were noted, except for stuffy nose, dizziness, and headaches. Vildagliptin is next in line to be approved by US. food and drug administration waiting on further clinical trials testing its effect on renally impaired patients. Recent reports of skin rashes necessitated additional safety analyses with Vildagliptin.

Incretin-based therapies

The two major incretin hormones released from the Gastrointestinal tract which mimic glucocose-stimulated insulin secretion are Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin peptide (GIP). These hormones promote insulin secretion in response to increase in glucose. GLP-1 receptor agonists inhibit the secretion of glucagon and promote insulin release. Dipeptidyl peptidase enzyme inactivates GLP-1 and GIP. This inactivation has lead to the development of DPP-4 inhibitors (sitagliptin, vildagliptin) and the new DPP-4 - resistant GLP-1 analogs called exenatide (Byetta). Exenatide is a GLP-1 agonist that is administered twice daily by subcutaneous injection. This agent slows gastric motility and inhibits the secretion of glucagon. It

lowers post-prandial glucose levels, hence lowering HbA1C by 0.5 to 1 %. It was shown not to be associated with hypoglycemia, but it causes GI side effects such as nausea, diarrhea, and vomiting. Exenatide is effective in combination with sulfonylureas and metformin when treating type 2 diabetes.

Nelson P, et al. compared the efficacy of exenatide as a monotherapy in patients with type 2 diabetes versus the combination therapy of exenatide with metformin. The study included 99 patients in the group receiving exenatide 10 mcg twice daily, and 127 patients treated with exenatide 5 mcg twice daily plus metformin oral therapy. Exenatide monotherapy resulted in a decrease of HbA1C level of 0.1 %, and a decrease in fasting plasma glucose levels of 11 mg/dl. On the other hand, Exenatide plus metformin resulted in a decrease in HbA1C of 0.1 % and a decrease of 0.5 kg in weight. The main adverse events in both groups were mild to moderate gastrointestinal in nature. The results were that exenatide injected twice daily causes approximately similar decrease in HbA1C levels and body weight when compared to combination therapy with metformin.²⁹

Table 1: Features of FDA approved oral hypoglycemic therapies in type II diabetes.^{2,3,6,8}

Drug	Advantages	Disadvantages	Lowers HbA1C	Most commonly reported adverse events	Failure rate
Sulfonylureas (1 st & 2 nd generation: acetohexamide, glipizide, glyburide, glimepiride)	Inexpensive, improved lipid profile by lowering Triglycerides	Weight gain, and rare but severe hypoglycemia	1.5%	Rare allergies, SIADH can be caused by first generation and disulfiram reaction with alcohol	10-15%
Short-acting insulin secretagogues (nateglinide, repaglinide)	Lower triglycerides, uncommon hypoglycemia	Weight gain similar to hypoglycemia	0.6%-1.0 %	Experience limited	Not reported
Biguanides (metformin)	Metformin is only FDA approved oral diabetic in children more or =to 10 years. Lowers TG and total cholesterol, no hypoglycemia, no weight gain	Minimal effect on HDL, used as Monotherapy does not sustain HbA1C reductions.	1.5 - 2.0%	Gastrointestinal side effect (Diarrhea) minimized by XR form. Lactic acidosis occurs rarely .	10-15% similar to sulfonylureas
TZDs (pioglitazone, rosiglitazone)	Lower TG, and raises HDL, no hypoglycemia effect	Weight gain, elevated ALT levels, and edema noted.	0.5-1.5%	Gastrointestinal adverse effects at elevated dosages, rare liver failure, as we mentioned fluid retention (CI in class 3, 4 CHF)	Not known
Alpha-Glucosidase Inhibitors (acarbose, miglitol)	Lower TG, no hypoglycemia noted, as well as absence of weight gain	Minimal effect on total cholesterol and HDL levels.	0.5-1.0%	Gastrointestinal adverse effects such as bloating, and flatulence.	10-15% similar to sulfonylureas
DPP-4 Inhibitors (sitagliptin)	Neutral effect on weight, no hypoglycemia, no drug interactions	Minimal effect on total cholesterol and HDL	0.89%	Upper respiratory tract infection, headache .	Not reported
Inhaled Insulin (Exubera)	Rapid-acting insulin, first easily inhaled insulin, reduce FPG by 23mg/dl, no refrigeration needed, no batteries, easy technique jubbreathe	Contraindicated in smokers and in patients who stopped smoking less than 6 months ago , CI in COPD patients	1.4%	Respiratory adverse events mostly, PFTs should be checked, hypoglycemia, dry mouth	Not reported

Footnotes: a. TG - Triglycerides, b. FPG- Fasting Plasma Glucose, c. CI- Contraindicated, d. PFT- Pulmonary Function Test, e. CHF- Congestive Heart Failure, f. HDL- High density lipoprotein cholesterol, g.TZD- Thiazolidinediones, h. ALT- Alanine transaminase, SIADH- Syndrome of Inappropriate Antidiuretic Hormone

Exubera (Insulin human rDNA origin inhalation powder)

Exubera is the first FDA approved inhaled human Insulin indicated for treatment of diabetes mellitus. When used in type 2 diabetes, it can be used as monotherapy or combined with oral hypoglycemic agents. Insulin’s main action is regulation of the metabolism of glucose. It stimulates uptake of glucose by skeletal muscle and inhibits production of glucose by the liver thereby lowering concentrations of blood glucose. Exubera’s onset of action is close to rapid-acting insulin analogues, and it’s duration of lowering-glucose activity is comparable to subcutaneous regular human insulin. As far as preparation of Exubera it is a

unit dose blister with each unit dose containing 1 or 3 mg insulin dose. 1 mg blister is equivalent to 3 IU and a 3 mg is equivalent to 8 IU of subcutaneous insulin. One of the disadvantages of Exubera is that it’s contraindicated in smokers or in patients who have stopped smoking less than 6 months prior to starting Exubera treatment. The reason is that systemic exposure to insulin from Exubera is 2 to 5 fold higher in smokers compared to non-smokers.

As far as published clinical studies, Rosenstock J, et al. studied the effect of this inhaled insulin on glyemic control then added to oral combination therapy or used as a substitution for the oral combination therapy in type II diabetes.

Summary of studies of newer agents,^{15, 19,29}

Authors Journal/Year	Raz I, et al. Diabetologia, 2006	Rosenstock J, et al. Ann Intern Med, 2005	Nelson P, et al. Diabetes Technol Ther, 2007
Purpose	to measure the safety and efficacy of sitagliptin as monotherapy in DM type 2 and inadequate glycemic control on diet and exercise.	to assess the effect of inhaled insulin (exubera) on glycemic control when used alone or added to dual oral treatment (insulin sensitizers and secretagogues) after failing dual oral therapy.	to assess the effect of exenatide as a monotherapy in patients with type 2 diabetes.
Design	A randomized, double-blind, placebo controlled study	A randomized, open-label, controlled study.	Study A: randomized, double-blind, placebo controlled trial Study B: open-label extension of a short term study
Methods	-Total of 521 patients with a baseline HbA1C of 8.1 % were randomized in 1:2:2 ratio to be treated with placebo, sitagliptin 100 mg once daily, and sitagliptin 200 mg once daily. - Duration of the study was 18 weeks. - Patients age was: 27-76 years.	- Total of 309 patients with HbA1C level of 8 to 11% were randomized to receive exubera titrated to blood glucose given alone (n=104) or added to dual oral therapy (n=103) versus oral treatment alone (n=99). -settings included 48 outpatient centers in Canada and the US. -Duration of the study was 12 weeks.	-Study A included 99 patients with type 2 diabetes that were given either 10 mcg exenatide injected twice daily, 10 mcg injected once daily, or 20 mcg once daily or placebo for 28 days. -Study B included 127 patients with type 2 diabetes treated with diet and exercise or metformin. Patients did receive exenatide 5 mcg twice daily for 4 weeks, then 10 mcg for 26 weeks.
primary & secondary endpoints	primary endpoints: -HbA1C change, Fasting plasma glucose secondary endpoints: -Insulin ratio, markers of insulin secretion and beta cell function -hypoglycemia, GI adverse events, Hypoglycemia	primary endpoints: -HbA1C change from baseline to 12 weeks. secondary endpoints: -hypoglycemia, weight, lipid levels, pulmonary function, HbA1C < 7% and 8%, adverse events, insulin antibody binding.	primary endpoints: -HbA1C change, Fasting plasma glucose. Secondary endpoints: -hypoglycemia, and GI adverse events.
Results	-HbA1C was reduced by 0.60 % with sitagliptin 100 mg and by 0.48% with sitagliptin 200 mg when compared to placebo. -Fasting plasma glucose were decreased with both strengths of sitagliptin. - markers of insulin secretion and beta cell function were improved with sitagliptin. -sitagliptin had a neutral effect on body weight. - GI adverse events incidence and hypoglycemia was not different between sitagliptin and placebo.	-HbA1C was more reduced with inhaled insulin. HbA1C level of less than 7% was achieved by 32% (oral therapy plus exubera) and by 1% (oral therapy) of patients studied. -mild weight gain, hypoglycemia, insulin antibodies, and mild cough were more observed with exubera compared to oral therapy alone. -Pulmonary function was not different between the 2 groups studied.	-10 mcg exenatide injected twice daily for 28 days resulted in HbA1C decrease of -0.4 or 0.1% and fasting plasma glucose of 11 mg /dl compared to an increase of 0.1 % and 12.7 mg/dl in placebo. -Exenatide in the open-label study of patients treated for 30 weeks resulted in a decrease in HbA1C and body weight in patients that were treated with diet and exercise alone (0.2 %, 1.3 kg) compared to those treated on a background metformin (0.1 %, 0.5 kg). -No severe hypoglycemia was noted in both studies. -most noted adverse events were moderate Gastrointestinal effects in both studies (A and B).
Inclusion/exclusion criteria	Inclusion criteria: -Patients with type 2 diabetes. -HbA1C ≥ 7%, and ≤ 10% Exclusion criteria: -Patients < 27 or > 76 years of age. -patients with adequate glycemic control	Inclusion criteria: -Patients with type 2 diabetes. -HbA1C level of 8 to 11% receiving dual oral therapy. Exclusion criteria: -Patients with No clinically significant respiratory disease.	Inclusion criteria: -Patients with type 2 diabetes. -Absence of background pharmacotherapy in study A. Exclusion criteria: -Patients not receiving metformin or not on diet and exercise in study B, limitations: -no p-value given.
Limitations/strength	Limitations: -no p-value given -needs a longer treatment period. Strengths: -Randomized, double blind, placebo controlled trial. -good sample size. -proper utilization of statistical test: analysis of covariance.	Limitations: -Short study duration (12 weeks). -only patients with HbA1C levels of 8 to 11% were included. Exubera was strictly compared to two class categories (sensitizers and secretagogues). Strengths: -Randomized, placebo controlled trial. -p-value and confidence interval were included. - 48 centers in US and Canada.	Strengths: -randomized, double-blind, placebo-controlled in study A. -good sample studied for both trials. -No bias noticed in both studies.

The study was randomized open-labeled which is conducted for 12 weeks. Exubera alone as monotherapy as well as combined with other hypoglycemic agents (insulin secretagogue and sensitizer) alone in terms of reducing HbA1C levels from baseline. Furthermore, the Exubera group was superior as far as reductions in fasting plasma glucose. The primary endpoint measured was a change in HbA1C value from baseline to 12 weeks. Secondary endpoints included HbA1C values, lipid levels, weight gain, and pulmonary function. Pulmonary function was not different between the 2 arms.^{10,19}

Due to Exubera's rapid onset of action when used as a mealtime insulin, it should be taken 10 minutes prior to a meal. Also because of the effect of Exubera's effect on pulmonary function, pulmonary function test should be assessed before starting therapy. It is contraindicated in asthma and COPD as well as it is pregnancy category C. Studies were not performed in patients with hepatic or renal insufficiency but the dose may be reduced in these patients as with other insulin formulations. The manufacturer company of exubera which is Pfizer might pull this drug from the market in three months due to its bad marketing effects. Patients who have tried this product were unpleased and shocked by this news because they thought that inhalation exubera relieved them from painful injections.

Drugs in Development

Other Gut hormones continue to play a very big role in treating type 2 diabetes. These hormones influence our blood glucose levels, digestion, weight and appetite. Some of those hormones include glucagon-like-peptide-1 (GLP-1) which Liraglutide drug is derived from. Exendin-4 is another hormone similar to GLP-1 stimulating secretion of insulin in the islets cells slowing gastric emptying. Ghrelin is another hormone stimulating appetite also oxyntomodulin reducing appetite and intake of food just like Peptide YY all being targeted for future researches.²¹ Other data have been released on investigational drugs called Dapagliflozin and Sertgliflozin used to block blood sugar reabsorption in type 2 diabetes. Dapagliflozin have been studied showing to enhance values of fasting blood glucose over 14 days.

Furthermore scientists in the United States had shown that a protein called Calcineurin has a big impact in type 2 diabetes. This protein regulates 10 genes responsible for the disease, and it is key to the health of pancreatic beta cells producing insulin. Drugs that promote the activity of Calcineurin or NFAT (it is protein sidekick) might become a new treatment in type 2 diabetes where beta cells do not make enough insulin.²³ Another very important point to mention is that activation of calcineurin will enable scientists to make embryonic stem cells become cells that produce

insulin. Also other genes have been discovered to play a role in type 2 diabetes such as Calpain 10, and transcription factor 7-like 2 gene.²²

Discussion

The incidence of type 2 diabetes remains on the rise in the United States. Long term complications of the disease are extremely concerning thus appropriate therapy is highly recommended. Lifestyle modifications such as diet, exercise and weight reduction considered a part of non-pharmacological treatments are equally important to pharmacological therapies.²⁴

In the oral treatment of type 2 diabetes, five different classes existed which are sulfonylureas, short-acting insulin secretagogues, Biguanides, Thiazolidinediones, and alpha-Glucosidase inhibitors. The introduction of new oral therapies in the past few years has widened the range of possibilities for treating type 2 diabetic patients.

Selection of an appropriate pharmacological agent is based on characteristics of the patient, considerations of the cost, and glucose control levels. Combination of two or more oral anti-diabetic agents are often needed for disease management.^{2,4}

Sulfonylureas remain the mainstay of treating patients with type 2 diabetes especially in ones with diagnosis of disease at age of less than 40. It exists in combination therapies with metformin and TZDs making this class extremely effective to the fact that about 20 % of patients on sulfonylureas will need an additional agent. Short-acting insulin Secretagogues similar in mechanism of action as well as adverse effect profile to sulfonylureas have a rapid onset of action and should be taken with meals 2 to 4 times daily. This class is a good alternative for patients with severe allergy to sulfa. Repaglinide from this class can be used in combination with metformin. Metformin belonging to Biguanides is very effective in weight reduction thus reduce the risk of cardiovascular disease, and insulin resistance.

Based on numerous studies, Thiazolidinediones have an important impact when used earlier in type 2 diabetes patients. Due to the fact that biguanides and sulfonylureas do not have an effect on protecting beta cells function without providing a sustainable glycemic control.^{5,6} The main function of TZDs is preservation of function of beta -cell and maintaining for a long period the glycemic control as well as to prevent insulin resistance. Alpha-glucosidase inhibitors indicated as a monotherapy or in combination with sulfonylureas play a good role in preventing the breakdown of carbohydrates reducing their uptake.

The first dipeptidyl peptidase-4 inhibitor (DPP-4) sitagliptin, can be used as monotherapy in combination with diet and exercise in treating type 2

diabetes. It also can be used as a combination with metformin or TZDs. Through prolongation of the body's own incretin hormones, sitagliptin increases release of insulin and reduces glucagon. Data shows that a major advantage to Sitagliptin is its favorable safety profile when compared to other oral diabetic agents.¹⁷ Its absence of effect on weight and lack of adverse drug reactions and interactions makes it a very potential oral hypoglycemic agent in treating type 2 diabetes.

Incretin-based therapies such as exenatide have also played an important role in treating patients with type 2 diabetes. Exenatide binds to the GLP-1 receptor on the surface of pancreatic beta cells of the pancreas enhancing insulin secretion that is glucose mediated. It is also effective when used in combination with sulfonylureas, metformin, and TZDs.

Exubera is the first approved inhaled agent in the treatment of type 2 diabetes. In clinical trials, it significantly improved HbA1C in patients with type 2 diabetes not controlled with other Anti-diabetic agents (Insulin secretagogues, Biguanides, and TZDs). Exubera showed benefits when used as monotherapy or when added to other hypoglycemic agents. This new agent has offered a new look in HbA1C control and may be considered as an effective add on therapy or monotherapy in treating Type 2 diabetes.¹⁹ Finally, Exubera may be an appropriate choice in patients who are not smokers, non-asthmatics, and who do not have Chronic obstructive pulmonary disease.

CONCLUSION

Oral hypoglycemic agents have a very important clinical impact on treating type 2 diabetes. Many complications develop if the disease is not treated early enough and with the proper pharmacological agents. These complications include diabetic retinopathy, nephropathy, and neuropathy. Other cardiovascular risk factors must also be addressed in patients with type 2 diabetes. Old agents such as sulfonylureas, biguanides, TZDs, alpha-Glucosidase inhibitors, and short-acting insulin secretagogues, and combination therapies had a good impact on disease treatment. Sitagliptin, Exenatide, and Exubera offer a different effective and new approach in management of type 2 diabetes. The clinical benefits of all pharmacological agents become more complete when accompanied with non-pharmacological treatments.

REFERENCES

1. American Diabetes Association: Standards of medical care in diabetes-2006. *Diabetes Care* 29 (Suppl. 1):S4-42, 2006.
2. Bolen S, Feldman L, Vassy J, et al. Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus. *Ann Intern Med.* 2007 July 16; [Epub ahead of print]
3. Carroll MF, IZARD A, Riboni K, et al. Control of postprandial hyperglycemia: optimal use of short-acting insulin secretagogues. *Diabetes Care.* 2002 Dec;25(12):2147-52.
4. Nathan DM. Initial management of Glycemia in type 2 diabetes

- mellitus. *N Engl J Med* 347:1342-1349, 2002.
5. Inzucchi SE. Oral Antihyperglycemic therapy for type 2 diabetes. *JAMA* 287:360-372, 2002.
6. Colagiuri S, Cull CA, Holman RR, UKPDS Group: Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes? *Diabetes Care* 25:1410-1417, 2002.
7. Diabetes Prevention Program Research Group: Reduction in incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393-403, 2002.
8. Rosenstock J, Hassman DR, Maddar RD, et al. Repaglinide versus Nateglinide Monotherapy: a randomized, multicenter study. *Diabetes Care* 27:1265-1270, 2004.
9. Gerich J, Raskin P, Jean-Louis L, et al. PRESERVE-B: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. *Diabetes Care* 28:2093-2100, 2005.
10. Rosenstock J, Zinman B, Murphy LJ, et al. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes. *Ann Intern Med* 143:549-558, 2005.
11. Bailey CJ, Bagdonas A, Rubes J, et al. Rosiglitazone/metformin fixed dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24 week, multicenter, randomized, double blind, parallel group study. *Clin Ther* 27:1548-1561, 2005.
12. Scherthaner G, Matthews DR, Charbonnel B, et al. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. *J Clin Endocrinol Metab.* 2004 Dec;89(12):6068-76.
13. Chilcott J, Tappenden P, Jones ML, et al. A systematic review of the clinical effectiveness of pioglitazone in the treatment of type 2 diabetes mellitus. *Clin Ther.* 2001 Nov;23(11):1792-823; discussion 1791.
14. Scheen AJ, Clinical efficacy of acarbose in diabetes mellitus: a critical review of controlled trials. *Diabetes Metab.* 1998 Sep;24(4):311-20.
15. Raz I, Hanefeld M, Xu L, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as Monotherapy in patients with type 2 diabetes mellitus. *Diabetologia.* 2006 Nov;49(11):2564-71.
16. Hermansen K, Kipnes M, Luo E, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, Sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab.* 2007 Jun 26; [Epub ahead of print].
17. Rosenstock J, Brazg R, Andryuk PJ, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther.* 2006 Oct;28(10):1556-68.
18. Herman GA, Bergman A, Yi B, et al. The Sitagliptin Study 012 Group Tolerability and pharmacokinetics of metformin and the dipeptidyl peptidase-4 inhibitor sitagliptin when co-administered in patients with type 2 diabetes. *Current medical research and opinion* 2006 Oct;22(10):1939-47.
19. Rosenstock J, Zinman B, Murphy LJ, et al. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. *Ann Intern Med.* 2005 Oct 18;143(8):128.
20. Herman WH, Hoerger TJ, Brandle M, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 142:323-332, 2005.
21. Wade N. Gene increases diabetes risk, scientists find. *New York Times* 16 Jan 2006:1.
22. Grant SF, Thorleifsson G, Reynisdottir L, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 2006;38:320-3.
23. Lyssenko V, Almgren P, Anevski D, et al. Genetic prediction of future type 2 diabetes. *PLOS Med* 2005;2:e345.
24. Diabetes statistics. Bethesda, Md.: U.S. Dept. of Health and Human Services, Public Health Service, National Institutes of

- Health, NIDDK, 1995; NIH publication no. 96-3926.
25. <http://www.texasdiabetescouncil.org>: Glycemic Control Algorithm For Type 2 Diabetes Mellitus In Children And Adults/Accessed on July 25, 2007.
 26. Smilev D, Umpierrez G. Metformin/rosiglitazone combination pill (Avandamet) for the treatment of patients with type 2 diabetes. *Expert Opin Pharmacother*. 2007 Jun;8(9):1353-64.
 27. Pratley R, et al. Efficacy and safety of Vildagliptin in the elderly: Pooled analysis of 5 monotherapy studies. Presented at EASD 17-21 September 2007.
 28. Garber A, et al. Efficacy and tolerability of vildagliptin added to a sulfonylurea (SU) in patients with type 2 diabetes (T2DM). Presented at ADA, 22-26 June 2007; (Abstract 501-P).
 29. Nelson P, et al. The incretin mimetic exenatide as a monotherapy in patients with type 2 diabetes. *Diabetes Technol Ther*. 2007 Aug ;9(4): 317-26.