EXENATIDE AND ITS INDICATIONS FOR USE AMONG THE THERAPEUTIC OPTIONS AVAILABLE FOR TREATMENT OF TYPE 2 DIABETES:

By

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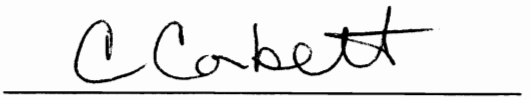
To the Faculty of Washington State University:

The members of the Committee appointed to examine the clinical project of JENNIFER JONES find it satisfactory and recommend that it be accepted.



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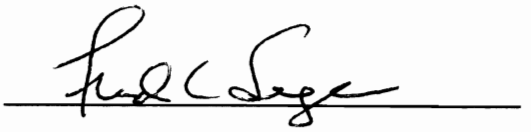

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EXENATIDE AND ITS INDICATIONS FOR USE AMONG THE THERAPEUTIC OPTIONS AVAILABLE FOR TREATMENT OF TYPE 2 DIABETES

Abstract

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The prevalence of type 2 diabetes continues to grow at near epidemic proportions in the United States. Diabetes is a costly disease with multiple associated complications. Type 2 diabetes accounts for up to 95% of all diabetes cases. Type 2 diabetes is a progressive disease. Initial therapy for type 2 diabetes is lifestyle modification, including nutritional therapy and weight reduction. As the disease progresses patients require oral antidiabetic agents and at least half eventually require insulin to maintain glucose control. Some of the traditional therapies available cause negative side effects such as hypoglycemia and weight gain. Despite the current treatment options available it is estimated that over 60% of people with type 2 diabetes are not achieving target HbA1c levels. New treatments are needed to help individuals with sub-optimal blood glucose achieve target levels. A new class of medications, incretin mimetics, was recently introduced. Exenatide is the first Food and Drug Administration approved drug in this class. The purpose of this paper is to evaluate the available data on exenatide and to review its indications for use among the therapeutic options available for people with type 2 diabetes. This paper will examine the economic, clinical and humanistic outcomes associated with exenatide based on available evidence. Studies have shown that exenatide is effective in controlling postprandial levels, reduces HbA1c levels and has the

added benefit of helping people with type 2 diabetes lose weight. Preliminary research suggests exenatide may possibly halt or reverse the progression of Beta cell loss, which is characteristic of type 2 diabetes. Nausea was a common side effect of therapy, which resolved over time. Exenatide has shown some positive results and may be beneficial as adjunct therapy for select patients with type 2 diabetes.

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Introduction

Diabetes is a metabolic disorder characterized by hyperglycemia as a result of impaired carbohydrate, fat and protein metabolism. Type 2-diabetes occurs when the pancreas does not make sufficient amounts of insulin to meet the body's requirements, or when there is insulin resistance. Insulin resistance is characterized by the body's inability to use glucose effectively. About 20.8 million people in the United States (U.S.) have diabetes (American Diabetes Association, 2006). Type 2 diabetes accounts for up to 95% of all diabetes cases and is more likely to occur in people who are over 40 years of age, overweight, inactive and have a family history of diabetes (National Institute of Diabetes, Digestive and Kidney Diseases, 2001).

Diabetes is the leading cause of kidney failure, non-traumatic limb amputations, blindness, and is a major contributor to coronary artery disease (CAD) and stroke. People with diabetes have twice the mortality rate of their non-diabetic counterparts. Heart disease and stroke account for 65% of deaths in people with diabetes. In 2002 diabetes was ranked the sixth leading cause of death (National Institute of Diabetes, Digestive and Kidney Diseases, 2002).

The general approach to diabetes management is to minimize the microvascular and macrovascular complications by preventing hyperglycemia and maintaining glucose homeostasis. The prevention of hyperglycemia can be achieved through lifestyle changes and/or pharmacotherapy.

The initial approach to treatment is lifestyle modification. Diet and exercise are the foundation for prevention and treatment of diabetes. A well balanced diet, emphasizing low-fat, low-cholesterol food choices is fundamental to diabetes treatment and self-care. Most people with type 2-diabetes are overweight and also need to concentrate on caloric restriction.

Consultation with a dietitian as part of a diabetes education program is a priority for patients with newly diagnosed diabetes (Pigman, Gan & Krousel-Wood, 2002).

People with type 2-diabetes generally benefit from increased activity. The purpose of exercise is to help reduce insulin resistance and improve insulin sensitivity. During physical exercise, glucose is taken up by muscle tissues at a rate seven to 20 times higher than at rest (Sato, 2003). The Diabetes and Prevention Program (DPP) was a major clinical study published in 2002, which compared diet and exercise to metformin monotherapy in people with impaired glucose control. The DPP demonstrated that diet and exercise interventions in people who are overweight and have impaired glucose control could significantly reduce their chance of developing diabetes compared to those who took metformin (Diabetes Prevention Program Research Group, 2002). This study supports the importance of diet and exercise in reducing insulin resistance and improving insulin sensitivity for those at risk of developing diabetes.

Adequate physical activity in relation to caloric intake reduces the risk of obesity, a major modifiable risk factor for developing type 2 diabetes. Likewise, lifestyle modifications, specifically diet and exercise, have been shown to be beneficial for patients with established type 2 diabetes. The Japan Diabetes Complications Study (JDCS) investigated the effects of a long-term lifestyle intervention on glycemic control and complication prevention in patients diagnosed with type 2 diabetes. Participants were given counseling and education on diet, exercise and behavior modification. At the conclusion of the study, participants in the intervention group achieved lower HbA1c levels than the control group. Differences in microvascular and macrovascular complications have not yet been published (Sone, 2002).

Pigman and colleagues investigated the effects of regular exercise on 300 patients receiving services through the Veterans Affairs Medical Center in New Orleans over a 30-month

period. Data was extracted from medical records and reviewed. Most participants who reported a regular exercise regimen did so through walking 30 to 60 minutes per day. The data showed that patients who reported a lack of regular exercise were 2.71 times more likely to have poor glycemic control than patients who reported exercising regularly ($p<0.004$). Diet and exercise is integral to the management of type 2 diabetes. Unfortunately, it is estimated that 60-80% of adults do not meet the recommended levels of physical activity needed to reduce chronic hyperglycemia (Pigman, 2002).

When diabetes is not well controlled by lifestyle changes, oral antidiabetic medications are the next therapeutic choice. There are three categories of oral medications used to treat hyperglycemia: (1) drugs that stimulate insulin secretion, (2) drugs that alter insulin action, and (3) drugs that affect the absorption of glucose. Drugs that stimulate insulin secretion, such as the sulfonylurea class, (e.g., glyburide), and those that alter insulin action, such as a biguinide (e.g. Metformin), are the most widely prescribed oral antidiabetic agents (Tierney, 2005). Oral antidiabetic agents are effective in controlling hyperglycemia initially, but these agents may fail to maintain glycemic control as the disease progresses. In a study by the United Kingdom Prospective Diabetes Study (UKPDS) Group, 53% of people with type 2 diabetes treated with oral antidiabetic medications required insulin therapy to maintain adequate glucose control after six years of treatment with oral agents (Dailey, 2005).

Insulin therapy is indicated when glucose control is not maintained with diet, exercise, and oral antidiabetic medications, and is generally used when other therapies fail to achieve adequate glucose control (Peyrot, et al. 2005). Both patients and providers have negative perceptions about starting insulin therapy. Patients often feel that being prescribed insulin means that their disease has advanced into a very serious stage. Some patients correlate insulin therapy

with a personal failure to adequately control their disease. Patients are also concerned about the negative side effects associated with insulin therapy, such as hypoglycemia and weight gain. Many express anxiety over the pain of injections and increased finger sticks (Hunt, Valenzuela & Pugh, 1997). They feel their life will be more restrictive and people will treat them differently (Funnell, Kruger & Spencer, 2004). Providers express barriers to prescribing insulin due to negative side effects, patient reluctance to start therapy, and concern about incorporating insulin training for patients into their clinical practice (Dailey, 2005).

Patients who are afraid of repeated needle injections with insulin therapy may have another option. An inhaled form of insulin, Exubera®, was recently approved by the Federal Drug Administration (FDA) for the treatment of type 1 and type 2 diabetes. An inhaled form of insulin may help to overcome resistance in some patients who need insulin therapy but are averse to injections. However, the drug will not replace the longer-acting insulin injections that many patients need. Recent studies suggest possible safety issues with inhaled insulin. The inhaled insulin causes some decline in lung capacity, indicating potential long-term risks (Peck, 2006) and is not recommended for everyone. Smokers who used inhaled insulin experienced excessive insulin levels (Himmelmann, et al. 2003). The FDA recommends that people who smoke or who have lung disease, such as asthma, should avoid using inhaled insulin (New FDA. 2006).

According to the Centers for Disease Control (CDC) (2005), only 15% of those with diabetes are able to control their diabetes with diet and exercise alone. Over 50% of those with diabetes take oral antidiabetic medications and 12% require the addition of insulin therapy. It is estimated that over 60% are not reaching the target HbA1c level, of <7% as recommended by the American Diabetes Association (CDC, 2005). For this reason new and improved treatment modalities are needed to control hyperglycemia in people with type 2 diabetes.

The first drug, in a new class of diabetes medications, incretin mimetics, may help people maintain glycemic control before needing to progress to insulin therapy. Exenatide (Byetta®) is an incretin mimetic and was recently approved by the FDA for the treatment of type 2 diabetes in people with sub-optimal glycemic control taking one or more oral antidiabetic agents. Exenatide was developed from the saliva of a poisonous reptile, the Gila monster. Incretins are hormones released by the gut, which stimulate insulin production in the pancreas after a meal. Exenatide is a synthetic adaptation of a peptide similar to the glucagon-like peptide (GLP-1), an incretin hormone secreted from the L cells in the jejunum and ileum (Freed, 2005).

In humans, incretins are released from the gut into the bloodstream following food ingestion and promote glucose-dependent insulin secretion from the pancreas. Exenatide is an incretin mimetic agent that mimics this process. Exenatide binds to and activates the human GLP-1 receptor, which leads to the synthesis of insulin and secretion of insulin from the pancreatic Beta cells by a mechanism working the cyclic AMP and/or other intracellular signaling pathways (Freed, 2005).

Exenatide has been shown to stimulate insulin secretion in the presence of elevated glucose (Kendall, et al. 2005). It restores the first phase insulin response, which is the first 10 minutes after food is ingested, that is usually lost in people with type 2 diabetes. It also lowers the production of glucagons after a meal and therefore reduces fasting and postprandial blood glucose. It also slows gastric emptying, which has a direct effect on reducing caloric intake and subsequently leads to weight loss (Freed, 2005).

The purpose of this paper is to evaluate the available data on Exenatide and to review its indications for use among the therapeutic options available for people with type 2 diabetes.

Review of the Literature

Zhou, Wang, Pineyro and Egan (1999) conducted a study demonstrating that glucagon - like peptide 1 (GLP-1) could stimulate chemically induced pancreatic tumor cells from rats to differentiate into insulin, pancreatic polypeptides, and glucagon-positive cells. Up to 50% of the cells differentiated into islet cells, the cells responsible for insulin production. In addition, Exendin-4, an analog of GLP-1, performed similarly, although it was ten times more potent.

Studies show that the first phase insulin secretion is reduced in people with type 2 diabetes. The first phase insulin response is defined as the sharp rise in glucose within the first 10 minutes after a meal has been ingested. Fehse (2006) conducted a study on 13 participants with type 2 diabetes and 12 healthy volunteers to evaluate the first and second phase insulin response when given a glucose challenge after being treated with Exenatide verses normal saline. The investigators found that the participants with diabetes who were given saline had decreased first phase insulin secretion compared with healthy volunteers. Participants with diabetes treated with Exenatide and given a glucose challenge had insulin secretory patterns similar to healthy participants, demonstrating a normal restoration of insulin secretion (Fehse, 2006).

Fineman and colleagues examined the activity and safety of exenatide in patients with type 2 diabetes currently treated with diet and/or oral antidiabetic medication in a randomized, triple-blind study. Participants (n=109) were randomly assigned to one of three subcutaneous injection regimens receiving Exenatide or placebo for a period of 28 days. The three treatment groups consisted of twice daily dosing of Exenatide (breakfast and dinner), twice daily (breakfast and bedtime), and three times daily (TID). Participants in the control group received the placebo injection TID. At the end of the 28 day study, HbA1c levels of <7% were achieved by 15% of Exenatide participants compared to 4% of placebo participants (Fineman et al., 2003).

DeFronzo and colleagues (2005) studied the ability of exenatide to improve glycemic control in patients with type 2 diabetes who were not well controlled while taking maximum effective doses of metformin. Investigators randomized 336 participants into two groups. One group administered exenatide 5mcg injected subcutaneously after a 4-week placebo lead in period. The other group administered 10mcg after a 4-week placebo lead in period. A third group received placebo injections throughout the study. All groups continued their metformin therapy. Of the participants studied, 46% of the 10mcg exenatide group, 32% of the 5 mcg exenatide group and 13% of the placebo group achieved target HbA1c < or equal to 7% ($p<0.01$). The addition of exenatide significantly reduced HbA1c levels ($p<0.002$) and weight in both treatment groups ($p<0.001$) compared to placebo (See Table 1). Exenatide produced some mild to moderate gastrointestinal side effects that decreased over time. Hypoglycemic sequelae was not increased with the addition of exenatide therapy (DeFronzo et al., 2005).

Buse and colleagues (2004) studied the ability of exenatide to improve glycemic control in patients with type 2 diabetes who were taking maximum effective doses of sulfonylurea and still not well controlled. Investigators studied participants over a 30-week period. Participants ($n=377$) were randomized into three groups, arm A, arm B and placebo. Participants in arm A administered exenatide 5 mcg twice daily subcutaneously after a 4-week placebo lead in period. The arm B group had a 10mcg twice-daily dose of exenatide. The third group received placebo injections. There were 41% in the 10 mcg group, 33% in the 5mcg group and 9% in the placebo group with achieved target HbA1c levels less than or equal to 7% ($p<0.001$). Fasting plasma glucose decreased in the 10mcg group compare with the placebo group ($p<0.05$). The exenatide arms showed significant dose dependent reduction in HbA1c levels ($p<0.001$), and the 10mcg exenatide arm showed significant weight loss ($p<0.05$) compared to placebo (See Table 1). The

most common side effect from the exenatide was gastrointestinal upset. No significant hypoglycemia was reported (Buse et al., 2004).

Kendall and colleagues (2005) studied the ability of exenatide to improve glycemic control in patients with type 2 diabetes who were not well controlled while taking maximum therapeutic doses of combined metformin-sulfonylurea therapy. Participants (n=733) were randomized into four groups. For this 30 week study group A received exenatide injections of 5mcg BID for the duration of the study. Group B received exenatide injections of 5mcg for a 4-week period, which then increased to 10 mcg BID for the duration of the study. Group C and D consisted of placebo injections with volumes equal to those used in groups A and B. Investigators measured changes in glycemic control based on HbA1c, fasting and postprandial plasma glucose concentrations, body weight and safety (Kendall et al. 2005).

At the conclusion of the study HbA1c changes from baseline were significantly reduced ($p<0.0001$) in the exenatide treatment arms (See Table 1). In the studied participants, 27% of those in group A (5mcg) reached an HbA1c less than or equal to 7%. In group B (10mcg), 34% achieved the same benefit compared to 9% in the placebo groups ($p <0.0001$). Fasting plasma glucose concentrations were reduced in the exenatide groups compared to an increase in the placebo groups. Postprandial plasma glucose concentrations were reduced by 59% in group A, and 87% in group B, compared with < 1% decrease in the placebo group ($p<0.001$). Participants in groups A and B lost significantly more weight compared to the placebo group ($p<0.01$) (See Table 1). The most common side effect with exenatide was nausea, which improved over time. There was no correlation between nausea and weight loss. Paticipants who initially experienced nausea in the first eight weeks continued to lose weight throughout the duration of the study period and those who never experienced nausea still lost weight. The incidence of mild or

moderate hypoglycemia was 19% (5 mcg), 28% (10 mcg) and 13% (placebo) and seemed to correlate to higher doses of sulfonylurea treatment (Kendall et al., 2005).

Heine and colleagues (2005) studied the effects of exenatide compared to insulin glargine in 551 patients with type 2 diabetes that were not well controlled with metformin and sulfonylurea therapy. Results of the study showed both exenatide and insulin glargine reduced HbA1c levels by 1.11%. Exenatide reduced postprandial glucose more than insulin glargine ($p<0.001$). However, exenatide was less effective in achieving target fasting blood sugar (less than 5.6mmol/L) than insulin glargine ($p<0.001$). Participants in the exenatide group experienced nausea more frequently (57.1% compared to 8.6% in the insulin group). Exenatide was as effective as insulin glargine in improving long-term glycemic control and had added benefits of maintaining postprandial homeostasis ($p<0.001$), avoiding nocturnal hypoglycemia (0.9 event/patient-year compared to 2.4 events/patient-year with insulin glargine), and reducing body weight. Subjects receiving exenatide lost an average of 2.3 kg while those receiving insulin glargine actually gained an average of 1.8 kg (Heine et al. 2005).

Discussion and Implications

New medications must be evaluated holistically. Clinical, humanistic and economic outcomes should be considered when evaluating new treatment approaches (Mangiapane et al. 2005). Clinical outcome analysis measures reductions in morbidity, mortality or use of emergency room services related to the disease. Humanistic outcome analysis evaluates the effects and effectiveness of treatments considering patient behavior and effects on patient quality of life. Economic outcome analysis considers the total cost of medical care associated with treating a condition compared to the consequences of the untreated disease (Bootman, 2005).

Each of these approaches will be considered in evaluating the overall effectiveness and efficacy of exenatide therapy.

Clinical Outcomes

Exenatide has a fundamentally different mode of action than any existing diabetic medication. It has been shown to halt or reverse the progression of B-cell loss that is characteristic in type 2 diabetics (Holst, 2005). This raises the question of whether or not exenatide will do the same in human subjects. The fact that exenatide is achieving better glucose control over some of the current traditional therapies suggests that it has some B cell preservation mechanism.

According to Bastyr and colleagues (2000), a greater reduction in postprandial glucose was associated with a greater reduction in HbA1c levels. They concluded that more control of postprandial blood glucose levels improved overall glycemic control better than an emphasis on controlling fasting blood glucose levels. Exenatide is more effective in controlling postprandial blood glucose levels than insulin glargine (Heine et al. 2005), metformin and/or sulfonylurea therapy (Kendall et al. 2005). Exenatide differs from other antidiabetic medications because it has some signaling mechanism that stops insulin secretion in the presence of euglycemia, thereby stabilizing blood sugar levels, and reducing the risk of hypoglycemia (Holst, 2005).

Exenatide is effective in reducing HbA1c levels when added to metformin and/or sulfonylurea therapy. In patients failing to achieve glycemic control who are already receiving maximum doses of metformin, adding exenatide significantly improved glycemic control (DeFronzo, 2005). Sulfonylurea drugs provide safe and effective treatment for people with type 2 diabetes. However, in a group of patients failing to achieve glycemic control while being

treated with maximum doses of sulfonylurea, adding exenatide significantly improved glycemic control (Buse et al. 2004).

Exenatide, when added to metformin and/or sulfonylurea therapy had the benefit of producing weight loss. Sulfonylurea alone and in combination with metformin is associated with weight gain compared to exenatide, and eventually fails to provide adequate blood glucose control in the majority of patients with type 2 diabetes (Buse et al., 2006). Metformin tends to cause less weight gain than sulfonylurea (Riddle, 2000). Exenatide therapy resulted in greater weight loss in participants compared to metformin or sulfonylurea therapy while insulin glargine therapy resulted in weight gain (Heine et al. 2005).

Hypoglycemia is a common occurrence in oral antidiabetic and insulin therapy. Hypoglycemia tends to be most severe with sulfonylurea therapy and tends to be dose dependent. The overall incidence of mild to moderate hypoglycemia was 28% in the 10mcg exenatide group compared to 13% for the placebo, with the higher incidence of hypoglycemia occurring when participants were receiving the higher dose of exenatide along with maximum doses of sulfonylurea (Kendall et al. 2005). The incidence of hypoglycemia may be reduced in exenatide/sulfonylurea combination therapy by reducing the sulfonylurea dose (Kendall, 2005). There was no difference in hypoglycemic reactions in the exenatide and metformin groups (DeFronzo et al. 2005). Symptomatic hypoglycemic events were similar in number and severity when exenatide was compared to insulin glargine. However, nocturnal hypoglycemia was reduced with exenatide (Heine et al. 2005).

Gastrointestinal symptoms were associated with exenatide administration compared to metformin, sulfonylurea and insulin glargine treatment. Nausea was the most common side effect of exenatide therapy occurring early in treatment during the first four to eight weeks, and

subsided over time. Participants who did not experience nausea continued to lose weight suggesting that nausea was not a direct cause of weight loss (Defronzo et al. 2005). Exenatide slows gastric emptying and should be avoided in patients with gastroparesis or other gastrointestinal conditions that would interfere with its target cells (Freed, 2005)

There are several limitations to the research on exenatide. Most of the recent studies of exenatide occurred over a short duration of 30 weeks or less. No long-term studies of exenatide have been published and other potential long-term benefits and/or problems with exenatide therapy may yet be discovered as its use increases. Also, exenatide has not been studied or approved for use in children. Exenatide is classified as pregnancy category C and should be avoided in these patients unless the benefit outweighs the risk. The safety profile of exenatide in breastfeeding women is unknown and therapy should be avoided at this time. Studies suggest B cell proliferation and differentiation in animal subjects. Future clinical studies may determine if exenatide therapy will halt or reverse diabetes disease progression in humans. Currently, exenatide is recommended in people with type 2 diabetes who are failing to achieve glycemic control while receiving metformin and/or sulfonylurea therapy. Future research is needed to evaluate the role of exenatide as a stand alone therapy.

Humanistic Outcomes:

When considering adding exenatide to traditional therapy, the advantages and disadvantages of therapy must be weighed. Altering one's lifestyle by changing eating habits and exercising adequately to improve glycemic control may be a challenge for some people. Some people may not be able to exercise regularly because of time and/or physical limitations. Some may find meal planning inconvenient when faced with time constraints. In some patients diet and exercise changes may be partially effective but insufficient to achieve adequate glucose

control alone. The biggest advantage of lifestyle modification is that it is inexpensive and has a lower risk of hypoglycemia and eliminates the potential for side effects often associated with oral antidiabetic agents and insulin therapy.

Oral medications may be perceived as an easy alternative to diet and exercise. Patients may view them as a quick fix pill that facilitates control of the disease without the effort required to make lifestyle changes. More monitoring of blood glucose is necessary with oral medication management because of the increased risk of hypoglycemia. Patients may find oral medications less restrictive than injection therapy. Blood glucose monitoring is generally less intensive with oral antidiabetic medications compared to exenatide or insulin therapy (Freed, 2005).

Patient compliance with a given therapy may be partially determined by its side effects. Sulfonylurea and insulin are known to cause hypoglycemia and weight gain. Exenatide does not increase the risk of hypoglycemia and may actually cause weight loss, which is a desirable outcome for patients with type 2 diabetes. Exenatide's primary negative side effect is nausea, which tends to occur early in therapy and resolves over time (Kendall et al. 2005). Patient compliance may be improved with exenatide therapy due to the benefit of weight loss and reduced risk of hypoglycemia.

Patients often perceive insulin therapy as signal of end stage disease. The transition to insulin injections forces patients to confront the seriousness of their disease in a way that oral medications do not. Patients are also reluctant to start insulin therapy due to fear of adverse side effects, such as hypoglycemia and weight gain. Patients may need to inject insulin more frequently, such as at mealtime and bedtime compared to exenatide therapy. Insulin therapy also requires more intensive blood glucose monitoring via finger sticks. Providers tend to be reluctant to initiate insulin therapy due to the possible side effects, and concerns about patient

adherence to proper monitoring procedures (Peyrot et al. 2005). Exenatide can be added as adjunct therapy for people with type 2 diabetes who possess sub-optimal glucose control while avoiding some of the negative perceptions and side effects associated with insulin therapy. Despite the need for injections, exenatide may not carry the stigma associated with insulin therapy. However, in those cases when a patient experiences advancing disease progression requiring insulin therapy, the established exenatide therapy may help some patients transition to insulin therapy by acquainting them with blood glucose monitoring and injection therapy.

Exenatide has special delivery and storage requirements that may be perceived as restrictive. It is administered by injection via pre-filled pen-injector delivery system containing 5mcg or 10mcg dosages. Exenatide is administered twice daily, 30 minutes prior to breakfast and dinner. It must be refrigerated at all times. It cannot be frozen, and should not be exposed to direct sunlight (Freed, 2005).

Exenatide may require more glucose monitoring at the initiation of therapy until blood glucose is stabilized. Since it only stimulates insulin production when blood glucose is high, patients using exenatide do not have to increase their blood glucose monitoring compared to insulin. However, some patients may perceive these blood glucose monitoring requirements as more restrictive than with lifestyle modification or with oral medication alone (Freed, 2005).

Economic Outcomes

Diabetes is a costly disease. Economic costs associated with diabetes in 2002 were estimated at 132 billion dollars in the United States. Approximately 91.8 billion dollars were attributed to direct medical costs, of which 24.6 billion dollars were spent for the treatment of complications of the disease. It has been estimated that diabetes represents 2.5 to 15% of the annual health care budget (Daily, 2005).

There are also indirect costs associated with diabetes. Many people may not be able to continue working due to the progressive effects of the disease. Illness, disability, premature mortality can have a direct effect on productivity. Intangible costs, such as pain, anxiety, inconvenience and other factors, such as decreased leisure activity and mobility can directly affect quality of life (World Health Organization, 2002).

The cost of disease must be balanced against the cost of treatment. The use of prescription medication lowers total healthcare costs and can improve patient outcomes. It is estimated that for each dollar spent on a new medication, it lowers hospital spending by $4.44 (Bootman, 2005).

Oral antidiabetic agents like metformin and sulfonylurea drugs cost approximately $70.00 to $94.00 per month for the most popular brands prescribed (Tierney, 2005). Exenatide is relatively new and is more expensive than oral or insulin therapy. Exenatide costs approximately $147.00 for a 5 mcg dose and $172.50 for a 10 mcg dose per month (New drug approved, 2005) compared to insulin preparations, which cost between $30.00 per month for long acting Ultralente insulin, and $67.00 for short acting insulin aspart (Tierney, 2005). Exenatide is more expensive than traditional therapies and may not be covered by some insurance plans. The costs of exenatide therapy will need to be compared to its long-term benefits of improved weight control and improved glycemic control, which may well provide substantial long-term reduction in microvascular and macrovascular complications and resultant medical costs in patients with diabetes.

Lifestyle changes are the least expensive of all therapies and can produce beneficial effects on weight loss and insulin sensitivity. The Diabetes Prevention Program found the cost of lifestyle intervention including exercise classes was approximately $40 per month (Diabetes

Prevention Program Research Group, 2003). However, many people with type 2 diabetes are unable to maintain target glucose control with diet and exercise alone. Prescribing antidiabetic medications to those with poor glycemic control is necessary in preventing disease progression and its complications. Despite the addition of pharmacotherapy, all patients with type 2 diabetes should continue a diet and exercise regimen throughout the course of medication treatment because it increases the effectiveness of the other therapies.

Summary

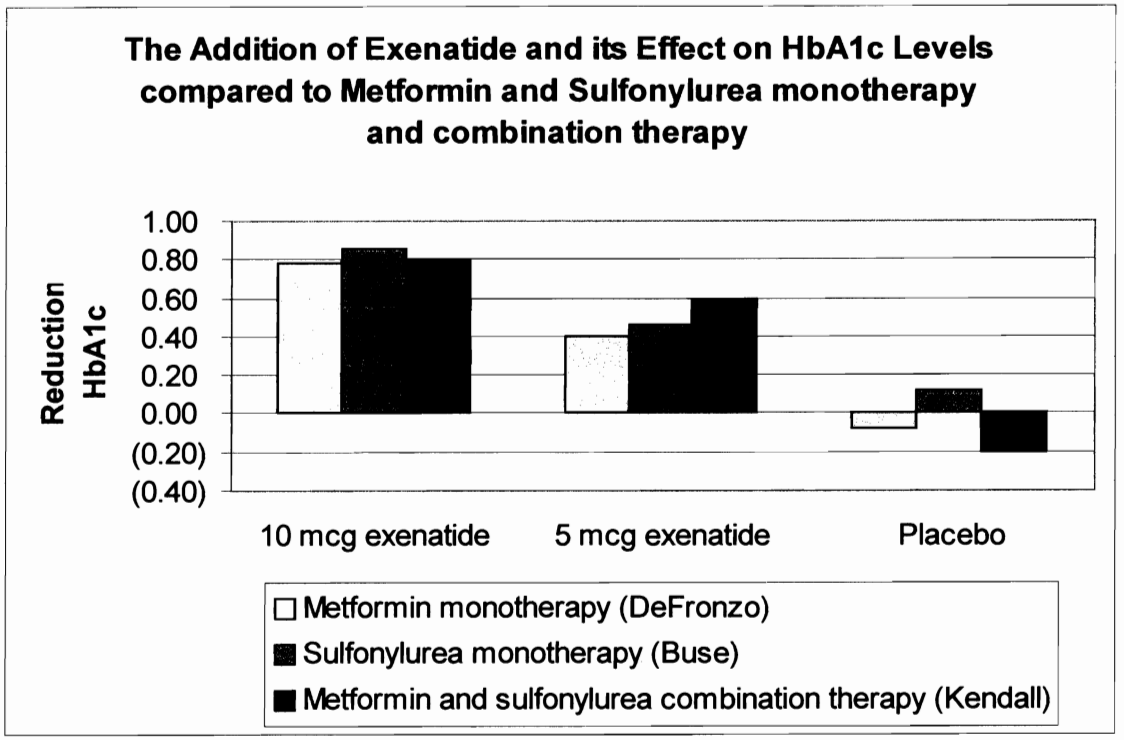
Initial research demonstrates that exenatide is beneficial as an adjunct therapy to oral antidiabetic agents. It has the potential to halt the progression of the disease, perhaps indefinitely delaying the need for insulin therapy for those with sub-optimal blood glucose control. Exenatide is indicated for those patients who are unable to achieve adequate glycemic control with lifestyle changes and oral anti-diabetic agents alone. Exenatide is effective in achieving glycemic control by reducing HbA1c levels, and at the same time helping participants lose weight. In addition, preliminary research indicates that exenatide may stimulate the production of new Beta cells. Exenatide requires injections twice daily, usually less than required by insulin therapy. Some nausea has been reported as a common side effect, which tends to resolve over time. The most positive features of exenatide are its tendency to reduce weight and the possibility that it may stimulate new Beta cell production in the pancreas. The primary negative features are its expense and the fact that it is administered by subcutaneous injection twice daily and requires glucose monitoring via fingersticks. As a new type 2 diabetes treatment option, exenatide may be especially desirable for overweight and obese individuals who are not meeting treatment goals, and who are willing to try an injectable drug, and have the means to afford it.

Table 1. Summary Results of Addition of Exenatide to Metformin/Sulfonylurea monotherapy/combination therapy.

Author	Size of Study	Study Design	Treatment	Reduction in HbA1c	Stat. Sig.	Weight Loss Compared to Placebo	Stat. Sig.
DeFronzo, 2005	N=272	Randomized, Triple-Blind, Placebo-Controlled	Exenatide 10mcg	-0.78%	P<0.002	-2.8 kg	P<0.001
			Exenatide 5mcg	-0.40%		-1.6 kg	
			Placebo	0.08%		0.0 kg	
Buse, 2004	N=129	Randomized, Triple-Blind, Placebo-Controlled	Exenatide 10mcg	-0.86%	P<0.001	-1.0 kg	P<0.05
	N=125		Exenatide 5mcg	-0.46%		-0.30 kg	NS
	N=123		Placebo	0.12%		0.00 kg	
Kendall, 2005	N=733	Randomized, Double-Blind, Placebo Controlled	Exenatide 10mcg	-0.80%	P<0.0001	-0.70 kg	P<0.01
			Exenatide 5mcg	-0.60%		-0.70 kg	
			Placebo	0.20%		0.00 kg	

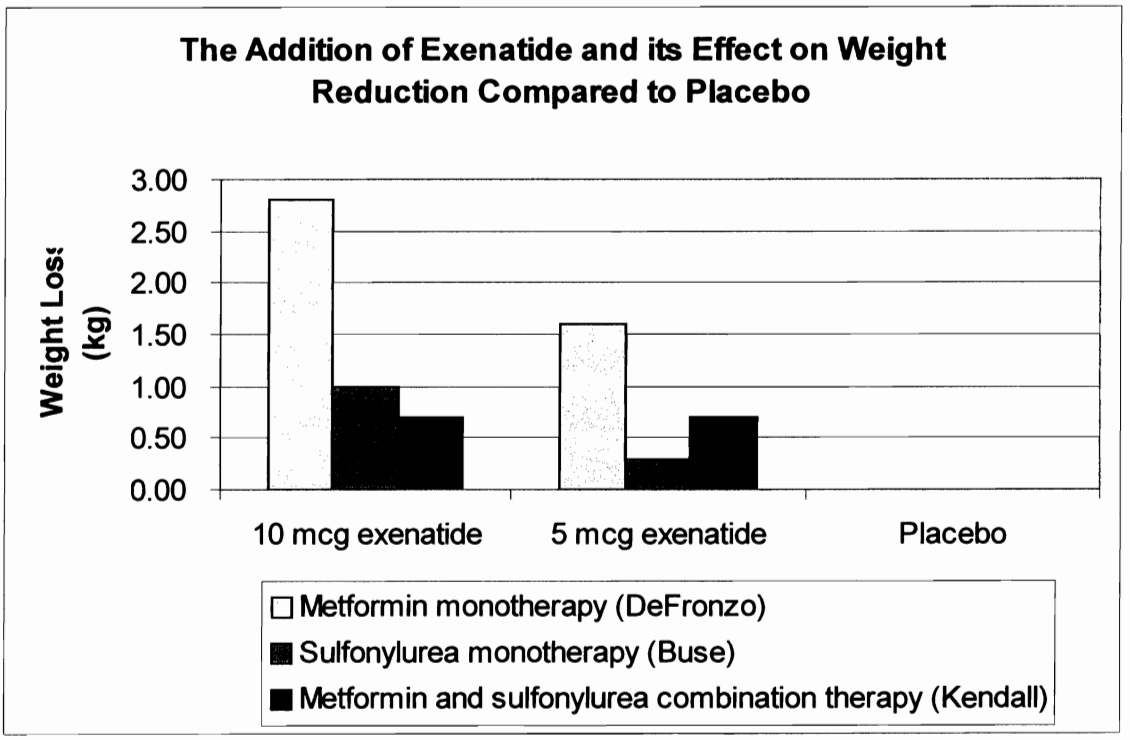
Data from DeFronzo et al. (2005), Buse et al. (2004) and Kendall et al (2005).

Figure 1



Data from DeFronzo et al. (2005), Buse et al. (2004), and Kendall et al. (2005)

Figure 2



Data from DeFronzo et al. (2005), Buse et al. (2004), and Kendall et al. (2005)

Figure 3

CHOICE OF ANTIDIABETIC MEDICATIONS

Drug	Advantages	Disadvantages
Metformin	Increases muscle insulin sensitivity Decreased hepatic glucose production May assist in weight loss. Useful in obese patients. Little hypoglycemia Less glucose monitoring	GI symptoms: diarrhea, nausea, vomiting, metallic taste. Risk of lactic acidosis in patients with renal or hepatic dysfunction.
Sulfonylurea	Increases endogenous insulin Generally well tolerated Little hypoglycemia Less expensive	Weight gain. Hypoglycemia
Insulin	Allows tighter glucose control Usually not associated with GI side effects Less expensive	Weight gain Hypoglycemia Nocturnal hypoglycemia Requires injection Requires daily glucose monitoring Negative perceptions associated with treatment
Exenatide	Decreased postprandial glucose Restored early insulin release Decreased glucagon Slowed gastric emptying Improved satiety B cell stimulation • Weight loss	GI side effects: Nausea, vomiting, diarrhea Hypoglycemia when used in conjunction with metformin or sulfonylurea. Requires injection twice daily. Injectible pens require refrideration Requires daily glucose monitoring Expensive

Data from Management of type 2 diabetes (2006) and Holst (2006).

References

American Diabetes Association, Inc. (2006). Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care,26,* 2528-2523.

Bastyr III, E.J. Stuart, C.A., Brodows, R.G., Schwartz, S., Graf, C.J., Zaugar, A. et al. (2000). Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. *Diabetes Care, 23,* 1236-1242.

Bootman, J.L. (2005). The value of pharmaceuticals. Retrieved February 16, 2006 from the World Wide Web; http://www.pharmrep.com/pharmrep/data/articlestandard/pharmrep/102005/150008/article.pdf

Buse, J.B., Henry, R.R., Han, J., Kim, D.D., Fineman, M.S., Baron, A.D. et al. (2004). Effects of exenatide (Exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care, 27*, 2628-2636.

Centers for Disease Control and Prevention (2005). *National Diabetes Fact Sheet: general information and national estimates on diabetes in the United States.* Atlanta, GA: Author.

Dailey, G. (2005). A timely transition to insulin: Identifying type 2 diabetes patients failing oral therapy. *Formulary* [electronic publication]. Retrieved February 24, 2006 from http://www.actmagazine.com/formulary/article/articleDetail.jsp?id=160377.

DeFronzo, R.A., Tatner, R.E., Han, J., Kim, D.D., Fineman, M.S., & Baron, A.D. (2005). Effects of exenatide (Exendin-4) on glycemic control and weight over 30 weeks in metfomin-treated patients with type 2 diabetes. *Diabetes Care, 28*, 1092-1101.

Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin, *New England Journal of Medicine,346*, 393-403.

Diabetes Prevention Program Research Group. (2003a). Costs associated with the primary prevention of type 2 diabetes mellitus in the diabetes prevention program. *Diabetes Care,26*, 36-47.

Diabetes Prevention Program Research Group (2003b). Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care, 26,* 2518-2523.

Fehse, F. (2006, January 7). Diabetes therapy; Exenatide augments insulin secretion in response to intraveneous glucose in type 2 diabetes. *Obesity, Fitness & Wellness Week,* pp. 330-331.

Fineman, M. S., Bicsak, T. A., Shen, L. Z., Taylor, K., Gaines, E., Varns, A. et al. (2003). Effect on glycemic control of exenatide(synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care*, *26,* 2370 2380.

Freed, S. (2005). Defeat diabetes: Can lizard spit diabetes??? Retrieved February 10, 2006 from http://www.defeatdiabets.org/Articles/drugs050504.htm.

Funnell, M.M, Kruger, D.F., & Spencer, M. (2004). Self-management support for insulin therapy in type 2 diabetes. *Diabetes Educator, 2*, 274- 280.

Heine, R.J., VanGaal, L.F., Johns, D., Mihm, M.J., Widel, M.H., Brodows, R.G. et al. (2005). Exenatide versus insulin glargine in patients with suboptimallyt controlled type 2 diabetes: A randomized trial. *Annuals of Internal Medicine, 143*, 559-571.

Himmelmann, A., Jendle, J., Mellen, A.Petersen, A.H., Dahl, U.L., Wollmer, P., et al. (2003). The impact of smoking on inhaled insulin. *Diabetes Care, 26*, 677-684.

Holst, J.J. (2005). GLP-1 receptor agonists for the treatment of diabetes. *International Diabetes Monitor, 17*(6), 11-18

Hunt, L.M., Valenzuela, M.A., & Pugh, J.A. (1997). NIDDM patients' fears and hopes about insulin therapy: The basis of patient reluctance. *Diabetes Care, 20*, 292-299.

Kendall, D.M., Riddle, M.C., Rosenstock, J., Zhuang, D., Kim, D.D., Fineman, M.S., et al. (2005). Effects of exenatide (Exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care, 28*, 1083-1092.

Management of type 2 diabetes (1998, March 25). *Therapuetics Letter.* Retrieved March 8, 2006 from http://www.ti.ubc.ca/pages/letter23.htm.

Mangiapane, S., Schulz, M., Muhlig, S., Ihle, P. et al. (2005). Community pharmacy-based pharmaceutical care for asthma patients. *Annuals of Phamacotherapy, 11*, 1817-1822.

National Institute of Diabetes and Digestive and Kidney Diseases (2001). Diet and exercise dramatically delay type 2 diabetes : Diabetes medication metformin also effective. Retrieved February 10, 2006 from http://www.hhs.gov/news/press/2001pres/20010808a.html.

National Institute of Diabetes and Digestive and Kidney Diseases (2002). Diet and exercise delay diabetes and normalize blood glucose. Retrieved February 11, 2006 from http://www.nig.gov/news/rp/feb2002/hhs-06.htm.

New drug approval notification (2005, June 20). *RxNews Newsletter*. Retrieved February 16, 2006 from http://www.rxsolutions.com/c/rxnews/rxnews_view.asp?Article+591&type+18

New FDA-Approved inhaled insulin underwent testing for effectiveness by memorial physicians. (2006). Retrieved April 9, 2006 from http://www.mhs.net/articles/editions/49/diabetes_treatment49.aspx.

Peck, P. (2006). ADA: Lung function still a problem with inhaled insulin. Retrieved March 14, 2006 from http://www.medpagetoday.com/index.cfm.

Peyrot, M., Rubin, R.R., Lauritzen, T., Skovlund, S.E., Snoek, F. J. & Matthews, D.R., et al. (2005). Resistance to insulin therapy among patients and providers: Results of the cross-national diabetes attitudes, wishes, and needs (DAWN) study. *Diabetes Care, 28*, 2673-2680.

Pigman, H., Gan, D. X., & Krousel-Wood, M. A. (2002). Role of exercise for type 2 diabetic patient management. *Southern Medical Journal*, *95*(1), 72-77.

Riddle, M.C. (2000). Managing type 2 diabetes over time: Lessons from the UKPDS. *Diabetes Spectrum, 13*, 194-196.

Sato, Y., Nagasaki, M., Nakai, N., & Fushimi, T. (2003), Obesity and diabetes: Pathophysiological mechanisms and therapeutic approaches, physical exercise improves glucose metabolism in lifestyle-related diseases. *Experimental Biology and Medicine, 228*, 1208-1212.

Sone, H., Katagiri, A., Ishibashi, S., Abe, R. et al. (2002). Effects of lifestyle modifications on patients with type 2 diabetes: The Japan diabetes complications study (JDCS) study

design, baseline analysis and three year-interim report. *Hormone Metabolism Reserves, 34*, 509-515.

Tierney, Jr. L.M., McPhee, S.J., & Papadakis, M.A. (2005). Current medical diagnosis & treatment 2005 (44th ed.). New York. Lange Medial Books/McGraw-Hill.

World Health Organization (2002). Diabetes: the cost of diabetes. Retreived February 21, 2006 from http://www.who.int/medicacentre/factsheets/fs236/en/.

Zhou, J., Wang, X. Pineyro, M. A., & Egan, J. M. (1999). Glucagon-like peptide 1 and exendin-4 convert pancreatic AR42J cells into glucagon-and insulin-producing cells. *Diabetes, 48,* 2358-2366.