Clinical Review of Incretin Based Therapies: Their Role in the Management of Type 2 Diabetes Mellitus.

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Type 2 Diabetes has become an epidemic in the United States; a disease that according to the CDC, in 2013, was the 7th leading cause of death among Americans. Even though there are various treatments available, it is not very clear when these agents are appropriate for individuals. Some agents have unfavorable side effects and can cause hypoglycemia. Newer agents, incretin based therapies, offer an alternative to controlling hyperglycemia. These agents not only help lower Hemoglobin A1C (HbA1C) values, but they also have the added benefits of weight loss, blood pressure control, and very low risks of hypoglycemia. There are two classes of incretin based therapies, GLP-1 Agonists and DPP-4 Inhibitors. Though these treatments have been on the market for several years, the use and knowledge of these drugs is still not prevalent. This review will discuss the role of incretins in diabetes treatment, the unique benefits these agents offer, their therapeutic efficacy, safety, side effects and reasons why these agents are not being utilized.

Background

Diabetes is a progressive disease that causes significant morbidity and mortality not only in the US but globally. An estimated 23.1 million Americans have diagnosed diabetes. The number of people with diabetes has quadrupled in the past 32 years (1980-2012), from 5.5 million to 21.3 million [1]. Globally every 6 seconds someone dies from complications related to diabetes, including cardiovascular, nephropathy, neuropathy and other organ complications [2]. The number of American adults diagnosed with diabetes each year has increased to 1.5 million new cases a year. According to this growing trend, by 2050 1 out of 3 Americans will have diabetes.

There are two types or forms of diabetes, Type 1 and Type 2. For this review, type 2 diabetes is the focus. The morbidity associated with Type 2 Diabetes can be significantly reduced by early interventions that help reduce glucose levels to a nondiabetic range. Life style modification, weight loss, oral hypoglycemic agents, insulin and combination therapies are some of the treatment options available to help control hyperglycemia. Even though there are a variety of therapeutic options for patients, the World Health Organization concluded that less than 50% of diabetics have well-controlled blood sugars on their current regimens. Cost, adverse side effects, lack of education on the long-term benefits, and medication administration, all play a major role in this deficit [1].

Newer agents known as “incretin” therapies, Glycogen Like Peptide Receptor Agonists and Dipeptidyl Peptidase 4, (GLP-1 and DPP-4), have proven to be effective in lowering glucose, are safe and provide unique benefits of weight loss, hypertension control and lipid reduction [3]. They have a lower incidence of hypoglycemia and have been proven to be as effective as other oral agents. They have effectively lowered HbA1C for patients not well controlled on monotherapy, when added to metformin [4]. They have also been proven to be as effective as other oral hypoglycemic agents as monotherapy when metformin is contraindicated [3]. Even with the added benefits and proven efficacy of incretin therapies, they are not being widely utilized by clinical providers. Uncertainties about the use and safety increased when the US Food and Drug Administration released a statement that certain incretin treatments increased mortality [5]. In 2016, another meta-analysis concluded that there were no clear overall differences in mortality in any of the hypoglycemic agents [6]. This clinical review provides guidelines for when to initiate dual therapy, the efficacy of GLP-1 and DPP-4, their safety, adverse side effects and the unique benefits these agents can offer to a patient with uncontrolled diabetes.

Epidemiology

Type 2 diabetes is the most prevalent form of diabetes and accounts for 90-95% of adult diagnosed diabetes in the US. Globally, 415 million people have diabetes and type 2 makes up 9-% of that population [2]. Americans 65 years of age or older are 25.2% more likely to have diabetes than younger Americans. In the US, American Indians, Hispanics, and African-Americans have a higher prevalence of type 2 diabetes. Adults with less than a high school education had a higher prevalence of diabetes, 12.6% compared to 9.5% of people with high school diplomas and 7.2% of individuals with more than a high school education. Risk factors include smoking, obesity, physical inactivity, hypertension, hyperlipidemia, and hyperglycemia [2].

Pathophysiology

Diabetes is a chronic metabolic condition comprised of several contributing factors that result in the body's inability to produce insulin, resistance to insulin action, and inadequate or excessive insulin secretion, all resulting in hyperglycemia. Approximately 50% of total daily insulin is secreted during basal periods, the remainder is secreted postprandially. The first phase of insulin secretion promotes peripheral consumption of the prandial load and usually occurs minutes after the consumption of a meal. During this phase, stored insulin is released and helps keep blood glucose from rising. If insulin storage is impaired, more time to produce insulin is required, which occurs during phase two. If phase two is still not able to control the high levels of glucose, this is considered impaired glucose tolerance. Blood glucose levels over 200 mg/dl after a meal is considered diabetes [2].

Clinical Diagnosis of Type 2 Diabetes

The American Diabetes Association (ADA) recommends that health providers start screening asymptomatic patients at >45 years of age, earlier if the patient has risk factors that increase their probability of acquiring diabetes. Risk factors include: 1) obesity; 2) a first-degree family history of diabetes; 3) hypertension; or 4) hyperlipidemia. One third of people with diabetes are asymptomatic and are unaware they have the disease. Patients with low risk factors sometime learn they have diabetes during a routine glucose screening with their primary care providers. Blood tests, such as Fasting Plasma Glucose (FPG), and a 2-hour glucose tolerance test can be used to diagnose diabetes (see table 1). The glucose tolerance test, however, is more inconvenient and expensive and is not used as often for clinical diagnosis. HbA1C is another blood test that can be monitored to measure the average amount of sugar in the bloodstream over the previous 90 days. In the Early Diabetes Intervention Program, the study demonstrated that an HbA1C was more sensitive than a glucose tolerance test in the early detection of type 2 diabetes for at-risk individuals. In 2009 The International Expert Committee recommended the use of HbA1C as a diagnostic tool and in 2010 the ADA adopted this criterion [7]. Once a person has been diagnosed with diabetes and begins treatment, HbA1C can be used every three months to monitor response to therapy. A HbA1C is an important indicator of how adequate a person's glycemic treatment

and management is over a period of months. A HbA1C can also help identify when additional treatments may be indicated for more appropriate glycemic control [1].

The American Diabetes Association criteria for diabetes

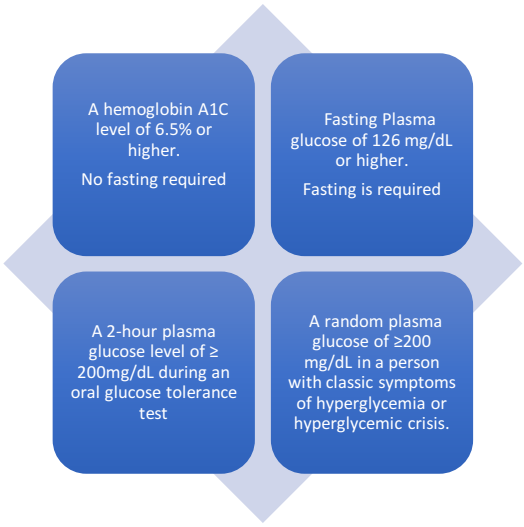

Figure1 [1] ADA Criteria for Diabetes

Targeted Glycemic Control

The ADA defines the therapeutic target for HbA1C as <7.0%. In order to achieve this HbA1C, a person's blood glucose levels need to average 70 to 130 mg/dl before meals and less than 180 mg/dl two hours after starting a meal. The level and duration of increased blood glucose in a diabetic increases the risk of diabetic complications. As glucose increases in the blood stream, the patient is in a state of hyperglycemia. Hyperglycemia can cause several complications for a diabetic. One serious condition that can occur due to hyperglycemia is ketoacidosis. Ketoacidosis can lead to seizures, coma and even death. Long term complications of diabetes include microvascular complications such as nephropathy, neuropathy, and retinopathy. Macrovascular complications can also be a long-term effect of

hyperglycemia, including coronary artery disease, peripheral arterial disease, and stroke. It is because of the risk of these complications that is vital for patients to maintain adequate control of their blood glucose. Lowering the target HbA1C at or below 7.0% has proven to help reduce both microvascular and macrovascular complications. An estimated 5-10% of patient fail to maintain a targeted HbA1C of 7% per year, even after successfully initiating monotherapy [2].

Guidelines for Initiation of Dual Therapy

According to the ADA and European Association for the Study of Diabetes (EASD) guidelines, the addition of a second medication should be initiated when a patient fails to meet the goal of <7%, three months after a trial of both life style modifications and metformin. Dual therapy should also be considered for all patients who have an HbA1C ≥ 9% [8]. Some type 2 diabetics can manage their diabetes with lifestyle changes, such as increasing physical activity and dietary modifications, to help with weight reduction. Sustained weight loss has proven to help reduce the need for pharmacological therapy. Individuals are more successful at lowering their glucose if they have a minimum weight loss of 7% of total body weight. The Standard Care of Diabetes Journal also recommended a minimum of 150 minutes of exercise per week to help achieve adequate weight loss [9]. Most type 2 diabetics are not able to control hyperglycemia with lifestyle modifications and require medications (Ref). Initial pharmacological therapy begins with an oral hypoglycemic agent such as metformin. Long standing evidence supports the use of metformin, a biguanide, as first line treatment for type 2 diabetes (ref). Metformin has proven safety and efficacy of reducing HbA1C, weight and cardiovascular mortality [10]. Not all patients can be effectively controlled on one therapy; eventually, because of the progressive nature of the disease, the use of an additional oral therapy or insulin is typically required.

Table 1. Comparison of medications for diabetes

Medication	Initial Dosing	Side Effects	ALC reduction	Weight Loss	Other Benefits	Cost
Biguanide MOS: Inhibits glycogenosis and gluconeogenesis.	Metformin: 500 mg PO BID Or 850 mg PO x 1 daily	1. Diarrhea 2. Lactic Acidosis in patients with cardiovascular, renal or hepatic dysfunctions. 3. B12 deficiency	1% to 1.5%	Weight neutral	1.Reduces CVD events 2.Prediabetes treatment	<$20.00 a month
Glucagon-like peptide-1 agonist MOA: Decreases glucagon secretion, slows gastric emptying and increases satiety.	Albiglutide: 30mg SC once weekly Dulaglutide: 0.75mg SC once weekly Exenatide: 5mcg SC BID Exenatide XR: 2mcg SC once weekly Liraglutide: 0.6 mg SC once daily x 1 week, then 1.2 mg SC once daily	1. Nausea 2.Diarrhea 3.Dosage modification for renal dysfunction. 4.Maybe associated with pancreatitis 5.Thyroid cell cancer in rodents only	1% to 1.5%	Weight loss	1.Decreased risk of hypoglycemia as monotherapy 2.Reduced postprandial glucose 3.Combination injectable	Albiglutide: $325 Dulaglutide: $490 Exenatide: $480 Exenatide XR:$475 Liraglutide: $430
Dipeptidyl Peptidase-4 inhibitor MOA: Prevents degradation of endogenous incretins increasing insulin secretion in response to elevated glucose. Decreases glucagon secretion and slows gastric emptying.	Aloglitin: 25 mg PO once a day Linagliptin: 5mg PO once daily Saxagliptin: 2.5 or 5 mg PO once daily Sitagliptin: 100mg PO once daily	1.CYP3A4 interactions 2.Maybe associated with pancreatitis	0.5% to 1%	Weight neutral	1.Well tolerated 2.Decreased risk hypoglycemia as monotherapy	Aloglptin: $310 Linagliptin: $330 Saxagliptin: $325 Sitagliptin:$330

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Diabetes Care2012;35:1364-79.

Metformin

In 1995, Defranzo and his colleagues demonstrated the efficacy and tolerability of metformin. In their "protocol 1" 143 patients received metformin compared to 146 who received placebo. Those who took metformin had a lower mean fasting plasma glucose of 189 +/-5 mg/dl vs 244 +/-6 mg/dl. The

patients who received metformin had an average HbA1C value of 7.1% +/-0.1% compared to the placebo group of 8.6% +/-0.2% [10]. Overall metformin is still recommended as first line treatment for Type 2 Diabetes by the ADA [12]. One of the biggest concerns for patients who are on metformin monotherapy is the gastrointestinal side effects. These side effects included diarrhea, dyspepsia, and flatulence. One study showed that the extended form of metformin reduced the number of patients who experienced these side effects but did not resolve them for all patients. Several studies have investigated incretin therapies, both as secondary options for patients who cannot tolerate metformin and as dual therapy for uncontrolled diabetics currently on metformin monotherapy [10].

Incretin Effect

The incretin effect in the human body involves the body's response to oral glucose that causes the increased insulin production in the body. The body's homeostasis is regulated by a vast array of hormones, among those Glucagon-Like Peptide (GLP-1) and Gastric Inhibitory Polypeptide (GIP). The GLP-1 hormone is released from the small intestine when a meal is ingested, which triggers insulin and glucagon release to help regulate blood glucose. Oral glucose has a higher stimulatory effect on the production of insulin in comparison to intravenous glucose. GLP-1 hormones bind to receptors in the pancreas and trigger the beta cells in the pancreas to release insulin. They also signal alpha cells to decrease glucagon secretion and causes the liver to decrease the release of glucose. Seventy percent of insulin secretion in a healthy human body comes from the incretin effect. GLP1 receptors can also be found in the hypothalamic center that controls energy intake. In type 2 diabetes there is an impairment or loss of function of the incretin effect [30].

GLP-1 Receptor Agonists

One of the more recently approved classes of therapeutic agents in the treatment of diabetes is incretin-based therapies. One of these therapies includes a GLP-1 receptor agonist. This medication works by binding to the receptors on GLP-1 when food enters the body and blood glucose levels rise. Like the

naturally occurring GLP-1 hormone, the agonist works in the gut to slow gastric emptying, thereby slowing the amount of glucose that enters the body. Delaying gastric emptying can help promote satiety and reduce the amount of caloric intake. In the pancreas, it causes beta cells to increase insulin release and suppress glucagon secretion. In the liver, it decreases endogenous glucose production. The route of administration for GLP-1RAs is by injection, with a half-life of up to 13 hours in comparison to the body's natural GLP-1 hormone's half-life of 2 minutes. The main role of the agonist is to increase resistance and time it takes dipeptidyl peptidase 4 to enzymatically degrade the glucagon-like peptide. These medications are only activated by the increase of blood glucose and reduce the overall chances of hypoglycemia [16]. Currently there are four FDA approved GLP-1 RAs, exenatide, liraglutide, exenatide LAR and albiglutide. Each has been studied as monotherapy and in combination with metformin.

Short Acting GLP-1AR

Exenatide was the first GLP-1 receptor agonist to be introduced in 2005 as an adjunctive treatment to diet and exercising for patients with Type 2 diabetes [15]. Exenatide therapy has been approved in the US to be used both as monotherapy and adjunctively with metformin. Exenatide helps to restore the first phase in insulin secretion and is administered prior to meals. It is not recommended for use after meals. In one triple, blinded placebo controlled trial of 336 patients, exenatide 5 μg twice daily was added to treatment for patients already receiving metformin at a dose of 1500mg daily [15] The study concluded that an overall reduction of 0.78% +/- .10% in the HbA1C of those receiving exenatide 10μg, compared to those receiving metformin and placebo 0.08% +/- .10% and an overall weight loss of -2.8 kg/+/- 0.5kg [15]. Of the 272 patients that completed the study 46% receiving 10 μg of exenatide twice daily achieved an A1C of ≤ 7% [15]. The most frequent side effects in the study were nausea, vomiting and hypoglycemia [15]. To help reduce nausea and vomiting a dose of 5 μg was recommended. To prevent hypoglycemia the injections should be administered at least 6 hours apart [15] In a 24 week, double blinded placebo-controlled, parallel-group study, exenatide was given to type 2 diabetes drug naive patients[18]. Patients were over the age of 18, maintained a diet and exercise regimen, were

randomly assigned to receive exenatide 5 μg exenatide 10 μg or placebo, each administered subcutaneously twice a day. At the end of the 24-week trial, exenatide was well tolerated[18] Patients sustained an improved HbA1C, reduced weight, improved blood pressure, and improved β cell function (REF). The authors concluded that it was an effective monotherapy option [21]. In another study comparing exenatide to metformin as monotherapy, exenatide has a greater reduction in HbA1C, -2.1 mg/dl vs -1.6mg/dl and greater weight loss -5.8kg vs -3.42kg[19]

Liraglutide

Liraglutide was the second GLP-1RA approved by the FDA in conjunction with lifestyle modifications. It has also shown efficacy in glycemic control both as monotherapy and in combination with metformin. Liraglutide delays absorption and resistance of DPP-4 degradation and is suitable for once daily administration independent of meal consumptions. In a study by Garber, 746 patients with T2DM, received monotherapy with liraglutide 1.2mg and 1.8 mg daily, and effectively lowered HbA1c by -.84% and -1.4% [31]. In 2009 a study by Nauck, in which liraglutide 1.2mg and 1.8mg were given in combination with metformin daily versus glimepiride 4mg in combination with metformin, all three arms?resulted in a similar reduction of HbA1c of 1.0%. Liraglutide decreased body weight by -1.8kg to -2.6kg compared to a 1.0 kg gain with glimepiride. Even though both these agents similarly decreased HbA1c, liraglutide had the added benefit of weight loss making it an ideal option for overweight or obese patients [20].

Long Acting GLP-1RAs

Exenatide LAR and albiglutide have both been studied as monotherapy and in combination with metformin. In a 26-week randomized, double-blinded trial by Russel –Jones in which exenatide LAR 2mg was given subcutaneously weekly compared to Metformin 2,000mg daily, HbA1c was reduced by −1.53% with exenatide LAR, and –1.48% with metformin [21]. Weight loss was similar with both treatments, -2.0kg [21]. In a 52-week placebo-controlled study of diabetics not well controlled with diet

and exercise and not currently receiving pharmacotherapy, were randomized to receive albiglutide 30mg, 50mg or matching placebo daily. At the end of week 52 patients receiving both 30mg and 50mg had a higher reduction in HbA1c compared to placebo. The most common side effects were injection site reactions [22].

DPP-4 –Inhibitors

Dipeptidyl Peptidase-4 is an enzyme the body naturally releases to inactivate both endogenous incretins, GLP-1 and GIP. DPP-4 is naturally released in order to maintain homeostasis and prevent hypoglycemia. DPP-4 enzymes regulate the amount of time incretins remain in the body. DPP-4 inhibitors bind to active sites of DPP-4 enzymes and prevent the degradation of incretins. By delaying the inactivation there is an increase of the sustained physiological action of incretins. There are four FDA approved DPP-4 inhibitors, sitagliptin, saxagliptin, linagliptin, and alogliptin. These drugs have proven to lower HbA1c both as monotherapy and in combination with metformin [23].

In a 24-week randomized double blind placebo controlled parallel group, type two diabetic patients with HbA1C range of 7.5-11% were randomized to receive one of 6 daily treatments. The 6 regiments included sitagliptin 100 mg/metformin 1,000 mg (S100/M1000 group), sitagliptin 100 mg/metformin 2,000 mg (S100/M2000 group), metformin 1,000 mg (M1000 group), metformin 2,000 mg (M2000 group) (all as divided doses administered twice daily [b.i.d.]), sitagliptin 100 mg q.d. (S100 group), or placebo. At the end of the trial sitagliptin reduced HbA1c in all the regiments, both as monotherapy and in combination with metformin with a decrease in baseline HbA1c of -0.83 (S100), -2.07% (S100/M1000), and -1.57% (S100/M2000). The overall adverse reactions among the groups were only modestly different. The highest incidences of these occurred in the high dose metformin monotherapy group. The overall incidence of hypoglycemia was low and similar across all groups. The one advantage that metformin had over sitagliptin was the weight reduction from baseline in patients -0.6—1.3 kg [24].

Table 2: 24-week study of Sitagliptin

Treatment	Number of patients	A1C<7%	Adverse reactions	Hypoglycemia
sitagliptin 50 mg/metformin 1,000 mg bid	178	66.00%	105	4
sitagliptin 50 mg/metformin 500 mg bid	183	43.00%	110	2
metformin 1,000 mg bid	177	38.00%	113	2
metformin 500 mg bid	178	23.00%	101	1
sitagliptin 100 mg q.d	175	20%	96	1
Placebo	165	9%	89	1

In a meta-analysis of randomized controlled trials, different DPP-4 inhibitors were compared to assess the effectiveness of reaching target HbA1c of 7% in patients with type 2 diabetes. The meta-analysis compared different arms in which each DPP-4 was used as monotherapy and in conjunction with metformin. A total of 18 RCT, with 3,646 patients, testing sitagliptin showed that 37% of patients achieved HbA1c of <7% with no differences in the eight arms. The mean decrease in HbA1c was .071%, -0.254 kg weight change and 3.1% incidence of hypoglycemia. Nine RCT with 1,608, testing the efficacy of saxagliptin showed that 38% of the subjects achieved the target A1C <7 %. There were 3 arms that used saxagliptin at 5mg and 3 arms at 10mg. The mean decrease in HbA1c was 0.8%, with -0.20kg weight change and 3.4% incidence of hypoglycemia [25].

In a 24 week study by *Del Prato et al*., 503 patients were randomized to receive monotherapy with either linagliptin 5mg/day or placebo. At the end of the 24 weeks linagliptin achieved a significant decrease in HbA1c compared to placebo. As monotherapy, the mean difference between the groups were -0.69%. The study also assessed the postprandial glucose effects of linagliptin 30 minutes after meals for 24 weeks. The adjusted mean change was -33.5 mg/dl with linagliptin compared to an increase with placebo of 24.9 mg/dl and placebo-corrected mean change of -58.4 mg/dl significantly favoring the DPP-4 inhibitor. As adjunctive treatment with metformin, linagliptin had a significant change in HbA1c vs

patients receiving metformin and placebo. The mean difference between groups was -.064%, and postprandial glucose was also assessed in this study and again showed a placebo-corrected mean of -67.1 mg/dl in the linagliptin group [26].

Alogliptin also proved to have a significant reduction in HbA1c and monotherapy. In a 26-week double blind, placebo-controlled study drug naïve patients, were randomized to receive once-daily dosing of alogliptin 12.5 mg, alogliptin 25 mg, or placebo. Changes in HbA1c were noted as soon as week 4, at the end of the trial there was a significant decrease in the groups receiving alogliptin. The group receiving 12.5 mg had a HbA1c reduction of -.56%, the 25-mg group had a decrease of -0.59% vs -0.2% reduction in the placebo group. As an adjunct to metformin, alogliptin proved to be more effective in lowering the HbA1c when compared to monotherapy. The 26 week randomized double-blinded placebo controlled study evaluated the safety and efficacy of adding the treatment to patients already taking metformin. They were randomized by a 2:2:1 ration to receive metformin + either, alogliptin 12.5, alogliptin 25mg or placebo. In the end both alogliptin groups lowered the A1c (-0.56% and -0.59%) greater than the *placebo group (-0.2%) [27].*

Discussion

Even though the ADA does not recommend GLP-1RA or DDP-I as first line treatment, these medications have been approved as alternatives for patients who cannot tolerate metformin. These drugs have favorable effects on weight, blood pressure and lipids overall decreasing the risk for cardiovascular events. GLP-1RA can also be taken as once a week which can help increase patient adherence compared to metformin or an adjunct insulin based therapy. Even though DDP-4 inhibitors are more weight neutral they are still effectively reducing HbA1c as both monotherapy and as adjunct therapy and can be taken orally. Incretin treatments also help preserve beta cell function, a mechanism that other mediations fail to maintain. They have proven to be more effective in lowering HbA1c and decrease the risk of hypoglycemia. Like all medications, incretin-based therapies have reported side effects. The most

common side effects are nausea, vomiting, diarrhea and injection site reactions. Most of these side effects can be managed by titrating medications to reduce the overall incidence of adverse side effects. Acute pancreatitis has also been reported in patients who have been treated with both GLP-1RA and DDP-4 inhibitors. Newer studies have shown that incretin-based treatments do not increase the risk of pancreatitis but there is an increased risk in patients who are obese with hypertriglyceridemia [11]. Medullary thyroid cancer (MTC) risk increases with GLP-1RA have been seen in rodents, but no cases have been proven in humans, and treatments are contraindicated in patients with personal or family history of MTC [29].

Metformin is still recommended as the first line treatment for T2DM by the ADA. Metformin has proven efficacy in reducing cardiovascular events by reducing weight, cholesterol, and triglyceride concentration. Overall all-cause mortality has been significantly reduced with the use of metformin [26]. Incretin therapies should be considered first line in patients who are not able to tolerate metformin. Incretins should also be considered as adjunctive therapy in uncontrolled metformin users, given their added benefits over other antidiabetic medications. They have proven to decrease the risk of hypoglycemia and can be taken daily or weekly, orally or by injection. Treatment should be tailored to meet the specific needs of each patient. These drugs have a higher cost compared to other second line treatments like insulin, sulfonylureas or thiazolidinedione, making them less affordable. It is important to ensure insurance companies cover these drugs given that they are not found in generic forms at this time. Other things to consider in choosing a treatment includes dosing frequency and finding the appropriate time for these medications to be administered during periods of elevated glucose. The ease of how these medications are administered should also be considered. Albiglutide and exenatide weekly require reconstitution before use. Patients should be educated before the medications are prescribed to ensure the patient is able to complete these additional steps. To avoid toxicity these medications should also be titrated according to their recommended labeling.

Clinical inertia by practitioners continues to be a barrier in properly treating type 2 diabetics. Better management of type 2 diabetes among health care providers must be achieved by overcoming clinical barriers. Some of these barriers include: 1) time and resource constraints, 2) fear of hypoglycemia with more aggressive treatment, 3) failing to set clear patient goals, 4) lack of clear clinical guidelines, 5) lack of clear treatment strategies, and 6) lack of knowledge in new diabetes treatments, such as incretin based treatments. Additional benefits of adding injectable incretin based therapies has been outweighed by providers in the belief that injectable medications are less acceptable in comparison to oral treatments. Improved awareness of newer therapies may help increase overall patient satisfaction and help patients to achieve HbA1c targets [29].

Conclusion

Incretin therapies are effective agents for the treatment of type 2 diabetes. They offer a variety of advantages, including weight loss and beta cell protection and reduce the risk of hypoglycemia. They also have cardiovascular benefits by reducing blood pressure, lipids and weight. They are also available in several forms of administration making them adaptable to personal lifestyles. Organizing a multidisciplinary team can help providers deliver a successful care plan and prevent clinical inertia. Patient adherence is linked to patient convenience, incretin based therapies have been designed to help address the complexity of these treatment regiments by combining multiple drugs in one pill or injection. Although these medications are proven effective as monotherapy and adjunctive therapy future studies are needed to define the long-term effect on safety and efficacy of these treatments and their impact on cardiovascular disease and mortality. Future studies should also include guidelines for practitioners on how to effectively assess and mitigate the risks associated with these medications.

Appendix.

Method: Data Sources: Searched PubMed Clinical Queries, PubMed, Cochrane Database of Systematic Reviews, UptoDate, Google Scholar, Trip Database. Retrieval was limited to Adults 18 years and older. Keywords were, Diabetes Mellitus, Diabetes Type 2 treatment, uncontrolled diabetes, poorly controlled monotherapy, adjunctive treatments, dual therapy for diabetes, metformin, glycaemic control, HbG a1c, exenatide, liraglutide, vildagliptin, sitagliptin, saxagliptin, alogliptin and linagliptin,GLP-1 Agonists, DPP-4 Inhibitors, insulin treatments, incretin effect. Focused on reviews, systematic reviews, meta-analyses, comparative studies, randomized and nonrandomized clinical trials, and National Guideline Clearinghouse. Search Dates March- July 2017. I used Cochrane Risk of Bias Tool to evaluate the validity of

Appendix table: Risk of Bias in included studies (High, Inconclusive, or Low Risk of Bias)

Study	*Random sequence generation*	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Reporting bias*
DeFronzo (2005)	*Low*	*Low*	*Low*	*High*	*High*	*Low*
DeFronzo (1995)	*low*	*High*	*Moderate*	*moderate*	*Moderate*	*Low*
Nauck (2009)	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*
Goldstein (2007)	*Moderate*	*Low*	*Low*	*Low*	*Moderate*	*Low*
Garber (2009)	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*
Russell-Jones	*Low*	*Low*	*Low*	*Moderate*	*Low*	*Low*
Nauck (2016)	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*
Capuano (2013)	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*
McGill	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*
DeFronzo (2008)	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*

Resources

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