

# Century of Evolution of Non-Insulin Therapeutic Options in Management of Diabetes

Nicholas Galioto<sup>1,2</sup>, Alexandra Jacob<sup>1</sup>

<sup>1</sup>Department of Family Medicine, the University of Iowa, Iowa, USA

<sup>2</sup>College of Osteopathic Medicine, Des Moines University, Iowa, USA

Email: ukabadi@gmail.com

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## Abstract

First recognized by the ancient Egyptians, the presentation and treatment of diabetes have dramatically evolved over the centuries [1]. Though the discovery of insulin 100 years ago changed the management of diabetes forever, most patients today are not insulin deficient, but overweight with a combination of insulin resistance and impaired insulin secretion [1]. While lifestyle changes can be very effective in improving glucose control, in the long-term most patients will eventually require medications to achieve adequate diabetic control [2]. For decades options for oral glucose lowering medications were limited, but in the past 25 years many more options have become available. The purpose of this article is to provide an overview of the existing oral and injectable (non-insulin) pharmacologic options available for the treatment of patients with type 2 diabetes.

## Keywords

Diabetes, Oral Drugs, Non Insulin Injectables 3

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## 1. Introduction

Since first being recognized by the ancient Egyptians around 1500 BC and treated with a preferred mixture of “water from the bird pond” elderberry, fibers from the asit plant, milk, beer, cucumber flower and green dates [1], the management of diabetes has dramatically evolved. In 2022 we will celebrate the 100<sup>th</sup> anniversary of insulin’s discovery, and unquestionably its discovery has completely changed the prognosis and management of diabetes. However, this discovery also led to a deeper understanding of the physiologic mechanisms of disease,

leading to the introduction of multiple medications either substituting or supplementing insulin in the treatment of type 2 diabetes. Though lifestyle changes and dietary modifications are known to be effective in improving glycemic control, most patients with type 2 diabetes will need pharmacologic assistance in achieving glycemic goals.

Currently there are ten classes of orally available pharmacological agents available to treat type 2 diabetes: 1) sulfonylureas, 2) biguanides (metformin), 3) meglitinides, 4) thiazolidinediones (TZD), 5) alpha glucosidase inhibitors, 6) dipeptidyl peptidase-4 (DPP-4) inhibitors, 7) bile acid sequestrants, 8) dopamine agonists, 9) sodium-glucose transport protein 2 (SGLT2) inhibitors, and 10) oral glucagon like peptide 1 (GLP-1) receptor agonists [2]. In addition to above oral anti-hyperglycemic agents, GLP-1 receptor agonists and amylin are available as injectables.

## 2. Sulfonylureas

Sulfonylureas were first introduced in the 1950s, but the hypoglycemic effects of synthetic sulfur compounds were first observed in 1937 by Ruiz and colleagues [3] [4]. The hypoglycemic effect of sulfur compounds was later confirmed in 1942 by Janbon and his colleagues, when noting hypoglycemia as a complication in the treatment of typhoid patients with para-amino-sulfonamide-isopropylthiodiazole [4]. In 1946 Loubatieres and colleges confirmed aryl sulfur drugs stimulated the release of insulin from pancreatic beta cells and therefore required some Beta cell function be present to have any effect on glucose levels [3] [4].

The first commercially available sulfonylurea was tolbutamide and was introduced in 1956 in Germany [3]. Other first generation sulfonylureas such as acetohexamide, chlorpropamide and tolazamide were quickly release. Nearly 25 years later, the more commonly known second generation sulfonylureas such as glyburide, glipizide and glimepiride were developed. These compounds were found to have a higher affinity for the targeted cellular receptor sites and thus proved to be far more potent compounds at lower doses [2]. Sulfonylureas mainly lower blood glucose levels by directly stimulating pancreatic beta cells to secrete insulin, but have other secondary effects that may also play a role in lowering blood glucose levels. These secondary effects include decreasing hepatic clearance of insulin, inhibiting glucagon secretion from pancreatic alpha-cells, and enhancing insulin sensitivity within the peripheral tissues [2]. Sulfonylureas are generally safe, inexpensive, and widely used as monotherapy or in combination with any other class of oral diabetic medications except meglitinides [2] [4]. The primary use limiting side effect is hypoglycemia. Since most sulfonylureas are metabolized in the liver and to some extent excreted by the kidney, hepatic and/or renal impairment can further increase the risk for hypoglycemia [2]. Overtime, patients on sulfonylureas may require the addition of other medications to maintain adequate glucose control. This secondary failure or lack of du-

rability is most likely due to beta cell exhaustion. Additionally, the weight gain that can be induced by sulfonylurea therapy can negatively impact glycemic control. Overall A1c reductions of 1% - 2% can be expected in responsive patients [2] [4].

### 3. Biguanides

French lilac or goat's rue (*Galega officinalis*) an herb was used in Southern and Eastern Europe during Medieval times as a folk remedy for the treatment of diabetes [3] [4]. The herb was found to contain guanadine, a compound with hypoglycemic properties but too toxic for clinic use [3]. Two synthetic diguanides were synthesized from this compound and used in the 1920s to treat diabetes, but were soon discontinued due to their hepatotoxic nature [3]. Interest in the biguanides continued and in the 1950s three biguanides were introduced: metformin, phenformin, and buformin [3]. Phenformin was widely studied in the United States, while metformin was studied in France, and buformin in Germany [4]. An increased incidence of lactic acidosis associated with phenformin and buformin, led to the withdrawal of these drugs from the market in most countries [4]. Metformin continued to be used in Europe, being reintroduced to the U.S. market in 1995 after 20 years of proven safe and efficacious use in Europe [3]. Metformin is the only clinically significant biguanide in use today and has become the most widely prescribed oral agent for the treatment of type 2 diabetes in the world [2]. Metformin is recommended as initial therapy for patients with type 2 diabetes by both the American Diabetes Association and the European Association for the Study of Diabetes [2]. Metformin works to reduce blood sugar levels mainly by decreasing hepatic glucose production and modestly increasing peripheral insulin-mediated glucose uptake [3] [4]. Typical reduction in A1c with metformin therapy is in the range of 1% - 2% [2] [3]. Metformin is contraindicated in patients with advanced renal and hepatic disease. Both chronic conditions increase risk for the development of lactic acidosis [2]. In 2016 the US Food and Drug Administration changed recommendations for metformin use in chronic kidney disease from should be avoided in patients with a creatinine level greater than 1.4 mg/dL in women and 1.5 mg/dL in men to contraindicated at eGFR less than 30 ml/min/1.73m<sup>2</sup> and not recommended to be started in patients with an eGFR less than 45 ml/min/1.73m<sup>2</sup> [5]. The most common side effect is gastrointestinal (GI). Nausea, diarrhea, and/or abdominal discomfort may occur in up to 50% of patients [2] [3]. These side effects are usually dose related and slow titration may help reduce occurrence. Prescribing immediate release metformin three times a day with food may also reduce GI related side effects. Extended release metformin causes fewer GI side effects and can improve tolerability in those patients who do not tolerate the immediate release formulation [2]. Long term metformin use has also been associated with vitamin B12 deficiency. Periodic testing of vitamin B12 levels should be considered, particularly in the setting of macrocytic anemia or neuropathy symptoms [6].

#### 4. Meglitinides

Mechanism of action is similar to the sulfonylureas in that these medications stimulate insulin release from pancreatic beta cells. This class of drugs has a rapid onset of action, short duration of action and is glucose dependent [2] [4]. Their pharmacokinetics make meglitinides particularly useful drugs in patients who eat erratically or have a need to specifically lower postprandial glucose levels [2]. Secondary to the rapid onset and short duration, meglitinides are administered up to 30 minutes prior to meals and maybe omitted if the patient is planning on skipping that particular meal. A1c reduction from meglitinides is approximately 1% - 1.5% [3]. Also similar to sulfonylureas, meglitinides can cause weight gain and hypoglycemia, but given their short duration of action, the risk for severe hypoglycemia is less [2]. However, meglitinides are metabolized in the liver and should be used cautiously in patients with impaired liver function or in combination with drugs that inhibit the cytochrome P450 enzymes, thus increasing the risk for hypoglycemia [2]. The first agent in this class, repaglinide was approved in 1997 and the second nateglinide in 2000 [4]. Repaglinide has shown to be slightly more effective in lowering A1c levels over nateglinide and is safe to use in patients with renal failure [7]. Neither has been shown to have a beneficial effect on cardiovascular outcomes [7].

#### 5. Thiazolidinediones (TZDs)

Thiazolidinediones are peroxisome proliferator activated receptor gamma agonists, promoting adipogenesis, tissue glucose uptake and insulin sensitivity [8]. Activation of these receptors leads to a decrease in fat accumulation within the liver, muscle and pancreas resulting in the reduction of insulin resistance and hepatic glucose production [2] [4] [8]. Troglitazone was the first thiazolidinedione to be approved for clinical use in 1997, but was quickly withdrawn from the market in 2000, due to idiosyncratic hepatic failure [3] [4]. Two other TZDs, rosiglitazone and pioglitazone were released in 1999. Both pioglitazone and rosiglitazone have each been linked to issues unrelated to glycemic control. Both agents have been linked to fluid retention and should be used cautiously in patients at increased risk for congestive heart failure [4] [7] [8].

Restrictions placed on rosiglitazone in 2010 over concerns regarding its cardiovascular safety were lifted in 2013 when reanalysis of the RECORD study concluded that patients treated with rosiglitazone did not have an increased risk of cardiovascular death, myocardial infarction, or stroke compared to patients taking other oral antihyperglycemic medications [4] [7] [8]. Pioglitazone has also been associated with a possible increased risk for bladder cancer [3] [4].

Though the data do not definitively support that pioglitazone significantly increases the risk of bladder cancer, the FDA recommends that pioglitazone not be used in patients with active bladder cancer or a history of bladder cancer [2].

A number of observational studies and randomized controlled trials have noted that long term treatment with TZDs decreased bone density, nearly doubling the

risk of fractures, particularly in women [2] [8]. The risk of fracture was similar between the TZDs and across age groups [2]. Though loss of bone density occurred throughout the body, fractures were more predominate in the upper and lower limbs compared to the lumbar spine [2].

TZDs can however have a positive effect on lipids depending on the medication chosen. Rosiglitazone can increase LDL and HDL cholesterol levels, and decrease serum triglycerides, if baseline levels are elevated [2] [8] [9]. Pioglitazone has little effect on LDL cholesterol, but increases HDL levels and decreases triglyceride levels [2] [9]. TZDs can also have beneficial effects on blood pressure and endothelial function [8] [9].

Whether used as monotherapy or in combination with other hypoglycemic drugs including insulin, TZDs can reduce A1c levels [2] [3] [7]. The glucose lowering effect of TZDs is gradual and maximal effect may not occur until 2 - 3 months after initiation of therapy [2] [8]. Though the onset of action may be more gradual, the durability of glycemic control with TZDs is more prolonged than either with metformin or sulfonylureas [2]. The glucose lowering efficacy of TZDs, along with potential benefits on blood pressure and lipids should be weighed against the potential disadvantages of edema, congestive heart failure and osteoporosis [2].

## 6. $\alpha$ -Glucosidase Inhibitors (AGIs)

AGIs work locally at the brush border of the small intestine by inhibiting

$\alpha$ -glucosidase enzymes, which prevents the breakdown of disaccharides and oligosaccharides into monosaccharides [4] [8]. Inhibition of brush border enzymes results in delayed carbohydrate digestion and absorption however, does not alter absolute absorption [4]. Thus AGIs are more effective at decreasing post-prandial glucose levels, while only demonstrating modest reductions in fasting glucose levels [4] [8]. The subsequent effect is only a modest reduction in A1c of 0.5% - 1% [4] [7] [8].

The first AGI developed was acarbose in 1995 [4] [8]. Subsequently miglitol and voglibose were introduced in some countries [8]. Due to only modest decreases in A1C, need for multiple daily doses at each meal and the undesirable gastrointestinal side effects (flatulence and diarrhea) related to their mechanism of action, these drugs are not widely prescribed [4] [8]. However, they have shown a greater beneficial effect in Asian or other populations whose predominate diet is rich in complex carbohydrates [8] [10].

## 7. Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists

The greater insulin stimulatory response to oral glucose in comparison to intravenous administration of glucose, is known as the “incretin effect”. The majority of the incretin effect is due to two gastrointestinal hormones: glucose dependent insulinotropic peptide (GIP) and glucagon like peptide-1 (GLP-1) [2]. It wasn't until the 1980s when the incretin-insulin pathway was fully understood and the

development of native glucagon-like peptide 1.

(GLP-1) was first studied in patients with type 2 diabetes [4]. In two key trials, patients with type 2 diabetes were injected with native GLP-1 and demonstrated a significant increase in insulin response with reversal of hyperglycemia [4]. Enhanced understanding of the incretin effect and the clinical findings in these initial trials led to the development of a drug class that utilized this mechanism by increasing GLP-1 production [4].

GLP-1 is a hormone secreted from the small intestine within minutes of a carbohydrate or fat containing load [3]. GLP-1 agonists result in a >10-fold increase in GLP-1 hormone levels, effectively working to lower glucose levels by potentiating glucose-dependent secretion of insulin and suppressing glucagon secretion. The high levels of GLP-1 hormone achieved have the additional benefit of slowing gastric emptying and promoting satiety [2] [7]. One of the first GLP-1 analogs was isolated from the venom of the Gila Monster (*Heloderma suspectum*) [4].

Exenatide, a synthetic form of exendin-4, was the first GLP-1 agonist to be approved for clinical use in 2005 [4]. Exenatide, as are other GLP-1's, is more resistant to dipeptidyl peptidase-4 (DPP-4) degradation thus having a longer half-life than native GLP-1 hormone [3]. Exenatide is available in two injectable formulations, a twice daily injection (Byetta) as well as a once weekly injection (Bydureon) [7]. Short acting GLP1 agonists include twice daily exenatide and lixisenatide [2]. Lixisenatide is administered as a once daily subcutaneous injection with the first meal of the day.

Long acting GLP1 agonists include weekly exenatide (Bydureon), liraglutide, dulaglutide and semaglutide [2]. Liraglutide was approved for use in 2010 and is approved for patients  $\geq 10$  years of age with type 2 diabetes [7]. Liraglutide is the only long acting GLP1 agonist that is a once daily injection [2]. Dulaglutide and semaglutide are both long acting GLP-1 agonists available as once weekly injections [2]. Semaglutide is also unique in that it has been recently released as an oral formulation (Rybelsus) [7]. It is important to note that exenatide and lixisenatide are contraindicated in patient with renal dysfunction [2] [7]. Unfortunately, these agents have been associated with adverse GI events particularly nausea, vomiting and diarrhea [4] [7] [11]. Concern regarding increased risk of pancreatitis and pancreatic cancer has been raised since the introduction of GLP-1 (and DPP-4) agonists. Extensive studies by the Food and Drug Administration showed no evidence for "pancreatic toxicity" of these medications [11]. In addition, several cardiovascular outcome studies have not demonstrated an increased risk of pancreatitis or pancreatic cancer among participants [11].

GLP-1 receptor agonists decrease A1c by 1% - 2% and can have the added benefit of weight loss [2] [7]. Several GLP-1 agonists have been shown to significantly reduce the risk of major adverse cardiovascular events (MACE) [11]. Multiple studies have examined each of the GLP-1's and their cardiovascular bene-

fits. Below is a summary of those major investigative trials for each of the GLP-1 agonists. The cardiovascular effects of exenatide were studied over a period of 3.2 years and included over 14,000 patients [12]. Exenatide was administered as a once weekly injection compared to placebo and composite endpoints of cardiovascular death, nonfatal-MI and nonfatal stroke were evaluated [11] [12]. Exenatide was determined to be non-inferior to placebo with respect to cardiovascular safety, nor was it superior in efficacy in reducing risk among patients with Type 2 diabetes with or without previous cardiovascular disease [12]. Simply put, exenatide was determined to be a safe addition to conventional therapy but offers no additional benefit in reduction of major cardiovascular events [12].

The effects of lixisenatide on cardiovascular outcomes in patients with type 2 diabetes were studied over 25 months and included over 6000 patients [13]. Lixisenatide was compared to placebo in patients who had recently (within 180 days) suffered a myocardial infarction or been hospitalized with unstable angina [13]. It was determined that lixisenatide, when added to conventional therapy, was not associated with a significant difference in rates of adverse cardiovascular events as compared to conventional therapy plus placebo [11] [13]. There were no significant differences in rate of hospitalization for heart failure, or the rate of death [13]. Lixisenatide was found to be noninferior to placebo when evaluating cardiovascular safety and thus is an effective adjunct to conventional hyperglycemic therapy [13].

The cardiovascular effects of semaglutide were studied over 2 years and included over 3000 patients [14]. Once weekly semaglutide was compared to placebo to determine effects on cardiovascular death, nonfatal MI and nonfatal stroke [14]. Patients with type 2 diabetes treated with once weekly semaglutide were found to have statistically significantly lower rates of cardiovascular death, nonfatal MI, and nonfatal stroke when compared to placebo [14]. Other indirect cardiovascular benefits included reduction in A1c, body weight and systolic blood pressure, which may have contributed to the positive outcomes [14].

The cardiovascular effects of dulaglutide were studied over a five-year period and included more than 9000 patients [15]. Dulaglutide has been shown to reduce blood glucose concentration, blood pressure, weight and albuminuria which lead to investigative trials regarding possible cardiovascular benefits [15]. When compared to placebo, dulaglutide reduced the risk of cardiovascular outcomes including cardiovascular death, nonfatal MI and most significantly non-fatal stroke [15]. Thus in summary, dulaglutide can be safely added to treatment regimen for patients with type 2 diabetes and may have the additional benefit of cardiovascular risk factor reduction [15].

Of the available GLP-1 agents in the United States, both semaglutide and dulaglutide seem to have the added benefit of decreasing the incidence of major adverse cardiac events in diabetic patient, while exenatide and lixisenatide dem-

onstrated no adverse effects on cardiovascular health, but also did not show any additional cardiovascular benefits.

## 8. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

The DPP-4 inhibitors result in elevated levels and activity of circulating incretin hormones, most notably glucose dependent insulinotropic peptides GIP and GLP-1 [2] [8]. GLP-1 and GIP are released in response to a carbohydrate or fat containing load but are quickly degraded by DPP-4 [8]. Because of their rapid degradation by DDP-4, GLP-1 and GIP have a very short half-life, <2 min and 5 - 7 min respectively [7] [8]. DPP-4 inhibition subsequently results in a 2 - 3-fold increase in postprandial active GLP-1 levels, in contrast to the more marked response seen with the GLP-1 agonists [2] [8]. The subsequent increase in GLP-1 and GIP levels potentiates glucose-dependent secretion of insulin and suppression of glucagon secretion [2] [7] [8]. As the DPP-4s have a more modest increase of GLP-1 hormone levels when compared to the GLP-1 agonists, they do not result in delayed gastric emptying or increased satiety but also avoid the nausea and vomiting associated with the initial onset of therapy [8].

The first DPP-4 inhibitor to be FDA approved was sitagliptan in 2006 [4]. Subsequently saxagliptan, linagliptin and alogliptan have been approved for monotherapy, dual therapy, and triple therapy as well as in combination with insulin within the United States [2] [7] [8]. Vildagliptan is an additional agent available in Europe [2]. On average DPP-4 inhibitors reduce A1c by 0.5% - 1% [4] [7] [8]. These agents have been associated with a small absolute increased risk of acute pancreatitis [2] [7]. DPP-4 inhibitor therapy has also been associated with an increased risk of reversible polyarthropathy, though relatively rare [2] [16].

DPP-4 agents do not have the same class effect on cardiovascular outcomes as the GLP-1 agonists or SGLT-2 inhibitors [2] [9]. Saxagliptan, alogliptin, sitagliptan and linagliptin when compared to placebo, did not increase or decrease rates of cardiovascular death, myocardial infarction or ischemic stroke [2] [9]. Interestingly, when compared to placebo in one trial, patients who were treated with saxagliptin were more likely to be admitted to the hospital with heart failure early in the treatment course, however no differences were noted after 12 months [2] [17]. Due to a similar effect observed with alogliptin, this has prompted the FDA to issue a warning regarding heart failure risk, especially in patients with cardiovascular and renal disease [11]. The impact of DPP-4 inhibitors on cardiovascular outcomes has been studied in five major trials including over 50,000 patients [11]. The conclusion from these multiple trials has shown this class of drugs as not increasing major adverse cardiovascular events (MACE), but they have also not shown any added cardiovascular benefits [11].

## 9. Sodium-Glucose Transport Protein 2 (SGLT-2) Inhibitors

SGLT-2 Inhibitors block glucose transporter, SGLT-2, which is responsible for



the reabsorption of 90% of filtered glucose [2] [4]. SGLT-2 Inhibitors decrease renal glucose reabsorption and increase urinary glucose excretion reducing fasting and postprandial blood glucose levels [7]. These agents can be used as monotherapy, in patients where metformin was not tolerated, in addition to other glucose lowering agents including insulin [8]. As these medications function at the renal tubule, their effectiveness is dependent on renal filtration of glucose and thus should not be initiated in patients with an eGFR <60 ml/min/1.73m<sup>3</sup> [8].

Currently there are 4 agents approved for use in the United States, canagliflozin, dapagliflozin, empagliflozin and ertugliflozin [7]. Canagliflozin was the first SGLT-2 inhibitor in 2013 [4]. These agents decrease A1c from 0.5% - 1% [2] [8]. One of the benefits of SGLT-2 Inhibitors is the ability to lower blood glucose levels independent of insulin action and therefore their effectiveness is not affected by insulin levels or insulin resistance [2] [8]. The cardiovascular benefits of SGLT-2 Inhibitors have been well studied. At this time there have been five large randomized studies of the effect of SGLT-2 Inhibitors on cardiovascular events and still others remain in progress [2]. In a population based cohort study (EASEL) in patients with type 2 diabetes and established coronary vascular disease, initiation of an SGLT-2 inhibitor was associated with lower rates of all-cause mortality, hospitalization for heart failure and major cardiovascular events, compared to initiation of non SGLT-2 inhibitor [7].

Studies regarding the potential benefit for SGLT-2 inhibitors on chronic kidney disease are emerging. Most recently, in July of 2021, dapagliflozin was the first SGLT2 inhibitor to be approved by the FDA for the treatment of adults with chronic kidney disease with or without type 2 diabetes [18].

Due to the mechanism of action of increasing urinary glucose, the most common side effect of SGLT-2 inhibitors is genital mycotic infections (balanitis and vulvovaginitis) [2]; however, an increased risk of urinary tract infections has not been consistently demonstrated [2] [8].

## 10. Amylin Agonists

Amylin, an endogenous neuroendocrine hormone was first discovered in 1987 [3] [4]. Amylin is co secreted with insulin by the pancreatic beta cells in response to food intake [19]. Patients with type I diabetes essentially have no amylin, whereas patients with type II diabetes have reduced amounts of amylin [3] [4]. The physiologic effects of amylin include suppression of glucagon secretion, reduction of hepatic glucose production, delayed gastric emptying and early satiety, leading to reductions in postprandial glucose levels [3] [19]. Pramlintide, a synthetic analog of amylin was approved in 2005 as an adjunct to preprandial insulin therapy [3]. For patients with type II diabetes, Pramlintide is initiated at a dose of 60 ug subcutaneously prior to each meal and increased to 120 ug subcutaneously after no significant nausea has been recorded for at least 3 days [2] [19]. A modest weight reduction of 1 - 3 kg was noted by patients; however the

significant nausea and only a modest decrease in A1c of 0.3% - 0.6% limited use [2] [3] [19]. Due to only minimal effect on A1c, significant nausea, need for multiple injections daily and the introduction of the GLP-1 receptor agonists, Pramlintide is rarely used today [2].

## 11. Bromocriptine

Bromocriptine is a dopamine agonist that has been used for many years in the treatment of Parkinson's disease and hyperprolactinemia. Only recently a quick release formulation of the drug (Cycloset) was approved in 2009 with a new indication as an antihyperglycemic [3] [4]. The mechanism of action is not fully understood but based on animal studies it is thought that the dopaminergic effects of the drug particularly at the hypothalamus, increases insulin sensitivity in liver, muscle and adipose tissue [2] [3] [20]. Oral administration of Bromocriptine is once daily within 2 hours of awakening [3] [20]. The starting dose is 0.8mg/day and can be titrated to a maximum dose of 4.8 mg/day [20]. The most common side effect was nausea, which can be lessened by administering with food. Other side-effects have included somnolence, fatigue, vomiting, headache and dizziness. Hypotension resulting in syncope can occur in patients on anti-hypertensive therapy [2]. Quick release Bromocriptine should be avoided in combination with strong Cyp3A4 inhibitors such as azole antimycotics or HIV protease inhibitors and dosages should not exceed 1.6 mg/day when used in combination with moderate inhibitors of CYP3A4 such as erythromycin [2]. Whether used as monotherapy, in combination with other oral hypoglycemic, or insulin, the addition of quick release Bromocriptine resulted in only modest decreases in A1C of 0.6% - 0.7% [2] [20].

## 12. Colesevelam

Colesevelam or Welchol is a bile-acid sequestrant primarily used to lower LDL-cholesterol was secondarily noted to also have a favorable effect on glucose levels. Because of this additional benefit, in 2008 the FDA approved colesevelam for use in patients with type II diabetes as an adjunct to diet and exercise [4] [8] [21]. Similar effects on glycemic control have been since noted with other bile acid sequestrants. The mechanism for glucose lowering is not completely understood but the leading theory centers on stimulation of the incretin pathway resulting in improved insulin secretion in the fasting and postprandial state [2] [22]. Effects on glycemic control are minimal, lowering A1c up to 0.5% when used in combination with metformin, sulfonylureas, pioglitazone, or insulin [2] [8] [21]. Side effects encountered are primarily gastrointestinal, with severe constipation being the most common and these agents are subsequently contraindicated in patients with a history of bowel obstruction and should be used cautiously in those patients with gastrointestinal motility disorders [2] [21]. Despite its favorable effect on LDL cholesterol levels, colesevelam increased triglyceride levels by 11% - 22% [8]. Because of the increase in triglyceride levels, coleseve-

lam is also contraindicated in patients with plasma triglyceride levels greater than 500 mg/dL or history of hypertriglyceridemia induced pancreatitis [2].

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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