5-2019

Glucagon-Like Peptide-1S compared to Sulfonylureas in the Treatment of Adults Diagnosed with Type II Diabetes Mellintus in Primary Care

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GLUCAGON-LIKE PEPTIDE-1S COMPARED TO SULFONYLUREAS IN THE TREATMENT OF ADULTS DIAGNOSED WITH TYPE II DIABETES MELLITUS IN PRIMARY CARE

by

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A Scholarly Project

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2019

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ACKNOWLEDGEMENTS

First, I would like to thank the UND PA faculty for their support and dedication to the program and the profession. To Jay Metzger, my advisor, thank you for your guidance and mentorship in my education and learning experiences. A sincere thank you to Dr. Michael Minnotte and Kara Petron for their assistance and input in this final project. Nobody has been more supportive to me in the pursuit of this project than the members of my family. Thank you for your love, support, and patience through this journey. I could not have done this without the support of Tyler, Mason, Rylan, my parents, and Amy and her family.

ABSTRACT

Type II diabetes mellitus (T2DM) is a prevalent disease in our country. Bullard et al. (2018) report approximately 21 million adults have T2DM in the United States. "The total estimated cost of diagnosed diabetes in 2017 is $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity" (Yang et al., 2018). Treatment of T2DM is individualized to each patient based on their co-morbidities, fiscal responsibility, and route of administration options. Sulfonylureas and Glucagon-like Peptide-1s (GLP-1) are two classes of antidiabetic drugs that are available for use as second line treatment options after metformin. This review of literature is from articles published in 2008 or later found in the following electronic databases: PubMed, Cochrane Database of Systematic Reviews, DynaMed Plus, ClincalKey, and Scopus. Articles included randomized control trials, systematic reviews, and meta analyses with participants being at least eighteen years old. The review found several benefits of GLP-1s for the treatment of T2DM. The risks of GLP-1s are not found to be as serious as the risks associated with sulfonylureas. Sulfonylureas demonstrate historical data for their use and are available in oral forms as opposed to GLP-1s which is newer but in an injectable form only. Overall, GLP-1s offer greater benefits with minimal side effects that are less severe than sulfonylureas. Limitations to this literature review include lack of articles having direct reviews of GLP-1s and sulfonylureas.

Keywords: glucagon-like peptide-1, sulfonylurea, diabetes mellitus, second line treatment

INTRODUCTION

The National Institute of Diabetes and Digestive and Kidney Diseases (n.d.) defines type II diabetes mellitus (T2DM) as a chronic condition that affects the way your body is able to metabolize glucose. With T2DM, the beta cells within the pancreas are able to produce insulin, but the body does not respond to the insulin normally or the body is resistant to the effects of insulin. Insulin is a hormone produced by the pancreas that controls the amount of sugar in the blood and allows the body to use sugar as a source of fuel. With T2DM, the body is not able to maintain a normal glucose level which affects multiple other body systems. Since there is no cure for diabetes, patients will need to control their blood glucose levels with diet and exercise. If that is not successful, antidiabetic drugs are utilized to supplement the body.

Some of the common antidiabetic drug classes are alpha-glucosidase inhibitors, biguanides (metformin), DPP-4 inhibitors, glucagon-like peptides (GLP-1), insulin, sodium glucose transporter 2 inhibitors (SGLT2), sulfonylureas, and thiazolidinediones. Each drug class acts on the body in a different way to achieve their effects. Due to the difference in mechanisms of actions of each drug, there are different benefits and risks of the drug classes. The purpose of this review is to determine if sulfonylureas or GLP-1s offer more benefits while minimizing the adverse effects for second line treatment of adults with T2DM in the primary care setting. It is anticipated that the benefits of GLP-1s will outweigh their adverse effects so that GLP-1s can be considered a superior treatment to sulfonylureas in the second line treatment of adults with T2DM in the primary care setting.

Statement of the Problem

With an increasing number of patients getting diagnosed with T2DM and newer drugs being developed, selecting an appropriate drug that offers the most benefit for the patient can be overwhelming. Further research is needed to identify which antidiabetic medication effectively lowers the A1c while providing additional benefits with minimal risks such as hypoglycemia.

Statement of the Research Question

In adult patients with uncontrolled T2DM in the primary care setting, does treatment with GLP-1s compared to sulfonylureas as adjuvant therapy to metformin offer more benefits while minimizing adverse effects?

REVIEW OF LITERATURE

Methodology

For this comprehensive review, five electronic databases were searched including PubMed, Cochrane Database of Systematic Reviews, DynaMed Plus, ClincalKey, and Scopus from July 14, 2018 to September 21, 2018. Specific terms searched include the following: sulfonylureas and type 2 AND (Review[ptyp] AND "last 5 years"[PDat]), sulfonylurea AND GLP1, sulfonylurea AND glucagon-like peptide-1, sulfonylureas AND second line, glucose-lowering medications for type 2 diabetes, management of type 2 diabetes in adults, GLP-1, and sulfonylureas. Works chosen for review were published after the year 2008 and included randomized controlled trials (RCTs), systematic reviews, and meta analyses. Sources excluded were those published prior to the year 2008, had poor design study, narrative reviews and studies that included patients under age eighteen.

Current Treatment Guidelines for Adults with T2DM

The American Diabetes Association (ADA) produces updated treatment recommendations after completing intensive evaluation of medical literature and input from the medical community and American Diabetes Association staff. This is completed on an annual basis. Their recommendations are graded on an A, B, C, or E level that is representative of the level of evidence to support the recommendation. A grade A recommendation for A1c goal in nonpregnant adults is < 7% (American Diabetes Association, 2018). Figure 1 displays treatment considerations based on the A1c results. The ADA also has a grade A recommendation for primary treatment of T2DM to be metformin unless it is contraindicated or not tolerated by the patient. The ADA states "in patients with type 2 diabetes and established arteriosclerotic cardiovascular disease (ASCVD), antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors" which is a grade A recommendation (American Diabetes Association, 2018, p. 24). Diabetes is an independent risk factor for ASCVD in which special consideration is needed when selecting pharmacologic therapies. Table 1 provides antidiabetic medication options while considering patient specific conditions for individualized treatment.

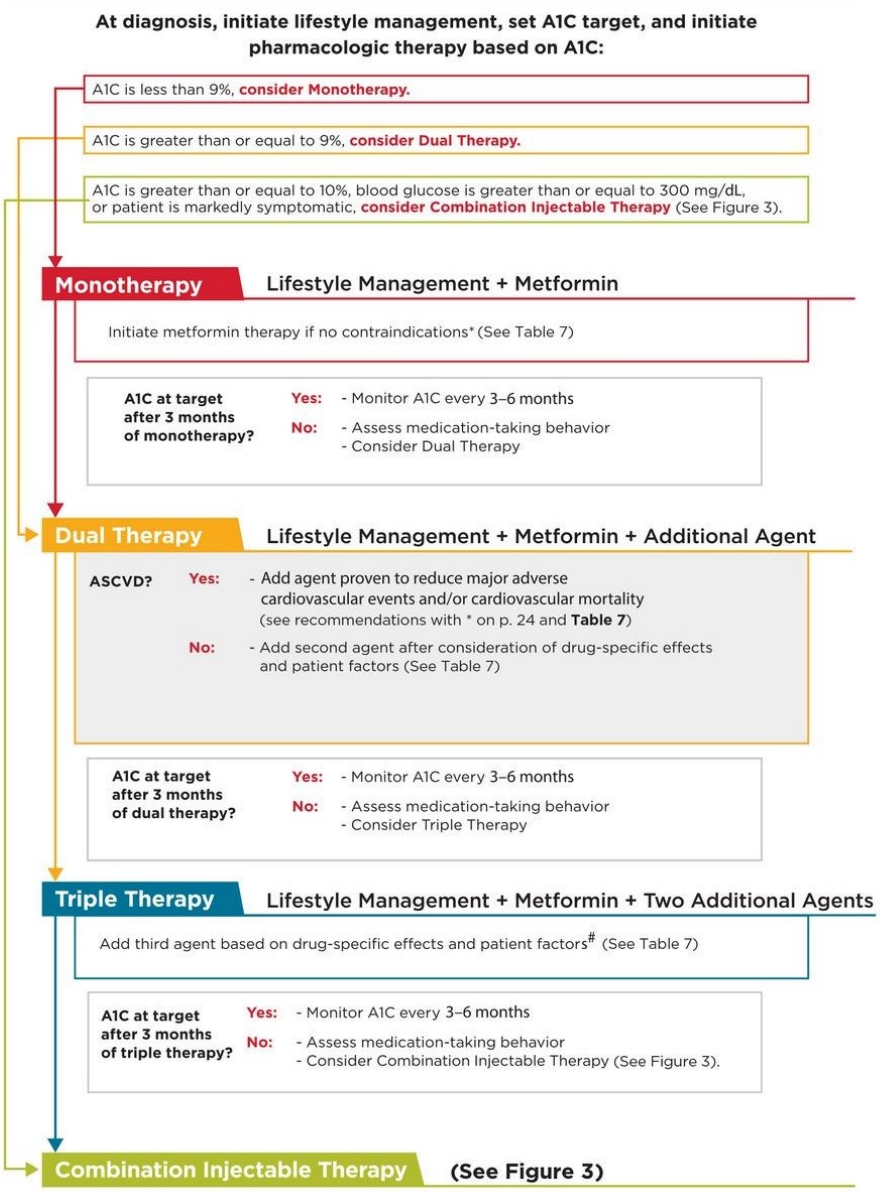

Figure 1. Reprinted from *Standards of medical care in diabetes – 2018 abridged for primary care providers*, by American Diabetes Association (2018), retrieved from http://clinical.diabetesjournals.org/content/36/1/14.full-text.pdf Copyright 2018 by American Diabetes Association.

Table 1

Antidiabetic treatment medications and patient considerations for T2DM

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required; can be used in renal impairment	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin **Human Insulin**	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Analogs						High	SQ			

Note. Reprinted from *Standards of medical care in diabetes – 2018 abridged for primary care providers*, by American Diabetes Association (2018), retrieved from http://clinical.diabetesjournals.org/content/36/1/14.full-text.pdf Copyright 2018 by American Diabetes Association.

Dynamed Plus (2018) reports a strong recommendation for adding a second drug if patients are on the maximum dose of metformin monotherapy and glycemic goals are not met. If ASCVD is present, adding a drug to reduce major cardiovascular events and mortality such as empagliflozin or liraglutide (GLP-1) is strongly recommended. If ASCVD is not present and A1c is not at goal, there is an ADA grade A recommendation for dual therapy which should be selected based on patient factors and drug characteristics. Antihyperglycemic drug options may include sulfonylureas, thiazolidinediones, dipeptidyl peptidase IV (DPP-4) inhibitors, sodium glucose cotransporter-2 inhibitor, glucagon-like peptide-1 receptor agonist, or basal insulin. In

the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review in 2016, 216 studies were reviewed by two reviewers regarding monotherapy and metformin-based combination therapies to lower the hemoglobin A1c (Maruthur et al., 2016). Combination therapies that were compared included sulfonylureas and GLP-1s combined with metformin. Metformin plus exenatide (GLP-1) was the preferred combination to lower the hemoglobin A1c (based on 3 short duration trials, pooled between group difference 0.26%, 95% CI 0.03%-0.48%). When considering body weight, metformin plus a GLP-1 was preferred (based on 4 trials, not pooled due to differences in dosing, drug type, and study duration; range of between group differences 2.4-12.3 kg). Neither sulfonylureas nor GLP-1s with metformin were preferred for long-term mortality (Dynamed Plus, 2018).

When adding a second drug to reduce major cardiovascular events and mortality and if ASCVD is present, GLP-1s such as empagliflozin or liraglutide are strongly recommended by the ADA (American Diabetes Association, 2018). If ASCVD is not present and A1c is not at goal, there is an ADA grade A recommendation for dual therapy, which should be selected based on patient factors and drug characteristics. Antihyperglycemic drug options may include sulfonylureas, thiazolidinediones, dipeptidyl peptidase IV (DPP-4) inhibitors, sodium glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, or basal insulin. According to the Endocrine Society of 2015 as a weak recommendation, adding GLP-1s or SGLT2 inhibitors should be considered when treating patients with T2DM who are overweight or obese (Apovian et al., 2015).

Montivida, Shaw, Atherton, Stringer, and Paul (2016) utilized the U.S. Centricity Electronic Medical Records to collect data on the usage of antidiabetic drugs for a longitudinal exploratory study from 2005 to 2016. This data was collected from primary and ambulatory care

systems in the United States. This data reports that of the 1,023,340 initially reviewed records of newly diagnosed T2DM between the ages of 18 and 79 years old, 357,482 records (subcohort 1) were identified for initiating a second-line medication after metformin. In the subcohort 1, sulfonylureas were the most popular second-line treatment despite a decrease in usage from 60% to 46%. GLP-1 usage for second-line treatment increased from 3% in 2006 to 7% in 2016. It was found that GLP-1 initiation was at the highest body mass index levels of all second-line treatment options. Montivida et al. noted some limitations to this study that lack of information on adherence, side effects, dosage changes, socioeconomic status, and insurance type.

Mechanism of Action of Sulfonylureas and GLP-1s

Grøndahl, Keating, Vilsbøll, and Knop (2017) provide information regarding the mechanism of action of sulfonylureas and GLP-1s. Sulfonylureas bind to the beta cells on the pancreas to block the K_{ATP} channels which increases insulin secretion. An increase in insulin secretion suppresses the secretion of glucagon leading to decreased blood glucose. GLP-1s bind to GLP-1 receptors which activates them in order to decrease blood glucose. They are designed to imitate endogenous GLP-1. Likewise, they are glucose-dependent which improves their safety.

Table 2 is adapted from an article by Thrasher (2017) that indicates the cellular mechanism of sulfonylureas is by blocking the K_{ATP} channels on the plasma membrane of beta cells which causes a primary physiologic effect of increasing insulin secretion. Conversely, the cellular mechanism of GLP-1s works by activating the GLP-1 receptors causing the physiological effect of increasing insulin secretion, decreasing glucagon secretion, slowing gastric emptying, and increasing satiety.

Table 2

Antidiabetic medication class specifics for GLP-1s and SUs

Class	Agents (Route of Administration)	Cellular Mechanism (s)	Primary Physiologic Action(s)	Advantages	Disadvantages	Cost
GLP-1 RAs	Albiglutide Dulaglutide Exenatide Exenatide XR Liraglutide Lixisenatide (SC injection)	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose dependent) • ↓Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety	• Rare hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some CV risk factors • Associated with lower CVD event rate and mortality in patients with CVD	• GI side effects (nausea, vomiting, diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High
SUs	Second generation Glimepiride Glipizide Glyburide (oral)	Closes K_{ATP} channels on β-cell plasma membranes	•↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk • Relatively higher HbA1c efficacy	• Hypoglycemia • ↑ Weight	Low

Note. CV = cardiovascular; CVD = cardiovascular disease; GI = gastrointestinal; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; SC = subcutaneous SU = sulfonylurea; XR = extended release. Adapted from *Pharmacologic approaches to glycemic treatment*, by American Diabetes Association (2017), retrieved from http://professional.diabetes.org/content/clinical-practice-recommendations Copyright 2017 by American Diabetes Association.

Kuhn, Park, Ghazi, and Aroda (2017) state that GLP-1 secretion is stimulated by nutrients entering the small intestine. This results in the insulin synthesis and secretion. The physiologic effect of slowed gastric emptying and increased satiety results in decreased caloric intake. A decrease in post-prandial glucose also results. Currently, GLP-1 administration is only subcutaneous.

Benefits of GLP-1s and Sulfonylureas in the Treatment of Uncontrolled T2DM

Chou et al. (2017) published a meta-analysis that included 40 trials with 70,162 participants on the long-term effects of ischemic heart disease in T2DM. Lower risk of myocardial infarcts was noted with those taking GLP-1s as compared to those taking sulfonylureas (OR = 0.48; 95% CI [0.27, 0.91]). There were no significant findings regarding

the risk of angina or effect on coronary artery disease when taking GLP-1s compared with other antidiabetic medications or a placebo. GLP-1s have demonstrated the ability to decrease several cardiovascular risk factors such as body weight, weight circumference, and blood pressure. These studies were limited to randomized controlled trials available in English. Most trials had less than one year follow-up.

Courtney, Nayar, Rajeswaran, and Jandhyala (2017) published a review that includes phase three clinical studies focused on GLP-1s with a duration of at least 76 weeks. The DURATION-1 study was able to show decrease in A1c (0.4-1.7%) and weight loss (0.9-5.3 kg) with long term treatment using a GLP-1. The low rate of incidence of hypoglycemia is an important consideration for long term treatment using an injectable medication. In the studies reviewed, only 4-21% of those that discontinued treatment of GLP-1s was due to adverse effects. Adverse effects tend to dissipate with continued treatment. Limitations to this review were due to the types of studies reviewed and lack of comparison of two GLP-1s.

Courtney et al. (2017) also reported outcomes regarding the cardiovascular benefits of GLP-1s. One of the studies reviewed was the LEADER trial which happens to be one of the largest and longest trials investigating the cardiovascular benefits of GLP-1s. This trial is a phase three, randomized, double-blind, placebo-controlled trial that included 9,340 patients with a minimum follow-up of 3.5 years. The GLP-1 (liraglutide) was compared against a placebo which demonstrated cardiovascular benefit from the GLP-1 with fewer deaths from cardiovascular causes, nonfatal myocardial infarction, or nonfatal strokes (95% CI [0.78, 0.97]; $p = 0.01$). Thirty-six months into the trial, the A1c was down by 0.4% in those treated with the GLP-1 (95% CI [-0.5, -0.3]). Weight loss was down by 2.3 kg more using GLP-1 treatment (95% CI, [2.0-2.5]).

The next trial reported by Courtney et al. (2017) was the ELIXA trial which evaluated the cardiovascular benefits of lixisenatide (GLP-1) in 6,068 T2DM patients. These patients were diagnosed with a myocardial infarction or hospitalization for unstable angina in the previous 180 days. The trial was a randomized, double-blind, placebo-controlled study with an average follow-up of 25 months. This trial demonstrated no significant difference in lixisenatide versus placebo (13.4% vs. 13.2%) regarding cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina (95% CI [0.89-1.17]; $p = 0.81$). The ELIXA and LEADER trials demonstrate the differences of pharmacokinetics of the two GLP-1s as the differing results regarding cardiovascular benefits within the same drug class.

Maruthur et al. (2016) reported a weight loss and decrease in systolic blood pressure by three to five mmHg without causing an increase in heart rate as benefits of GLP-1s. It is unknown if these changes in weight and blood pressure are enough to make a difference in the cardiovascular morbidity and mortality.

Risks of GLP1s and Sulfonylureas in the Treatment of Uncontrolled T2DM

Choby (2017) provided an update regarding pharmacotherapy in T2DM published in the FP Essentials journal.

Table 3

Adverse effects of GLP-1s and sulfonylureas

Class/Drug	Average A1c decrease (%)	Cost	Major Adverse Effects	Other Adverse Effects
GLP-1				
Exenatide (Byetta, Bydureon)	0.8 - 2	$500 – 520		Nausea, vomiting, diarrhea; avoid with history of pancreatitis
Liraglutide (Saxenda, Victoza)		$769		
Sulfonylureas				
Glimepiride (Amaryl)	0.4 – 1.2	$10 – 70	Hypoglycemia	Weight gain
Glipizide (Glucotrol)		$10 – 30		
Glyburide		$10 – 90		

Adapted from "Diabetes update: New pharmacotherapy for type 2 diabetes", by B. Choby, 2017, *FP essentials*, 456, p. 28-29. Copyright 2017 by AAFP.

As stated in Table 3 from Choby (2017) disadvantages of sulfonylureas are hypoglycemia and weight gain. Glyburide specifically has increased risks of hypoglycemia and cardiovascular mortality with long term treatment as compared with other sulfonylureas. Glyburide is not the recommended to be prescribed to elderly according to the recommendations from the Beers criteria. In the GLP-1 class, nausea, vomiting, diarrhea, and injection site reactions are some associated adverse effects. "Risks of increased calcitonin secretion, C-cell hyperplasia, and medullary thyroid cancer have been linked to sustained GLP-1 receptor activation in mice and rats" (Choby, 2017, p. 32). Literature suggests that GLP-1s do not have a significant increase in pancreatic effects, but labels currently recommend avoiding GLP-1s if patients have a history of pancreatitis and to discontinue use if the patient is diagnosed with pancreatitis while on a GLP-1. As noted in Table 3, there is a difference in cost associated between GLP-1s and sulfonylureas with GLP-1s being more expensive.

Douros et al. (2018) completed a population-based cohort study investigating the use of sulfonylureas as a second line antidiabetic drug and the risk of cardiovascular and hypoglycemic

events. The study began with 77,138 T2DM patients on metformin. A total of 25,699 patients added or switched to sulfonylureas. The mean follow-up was limited at 1.1 years. At that time, sulfonylureas demonstrated an "increased risk of myocardial infarction (incidence rate 7.8 vs. 6.2 per 1000 person years, hazard ratio 1.26, 95% CI [1.01,1.56]), all cause mortality (27.3 vs. 21.5, hazard ratio 1.28, 95% CI [1.15,1.44]), and severe hypoglycaemia (5.5 vs. 0.7, hazard ratio 7.60, 95% CI [4.64, 12.44]) compared with continuing metformin monotherapy" (p. 1). Table 4 also identifies the differences from adding a sulfonylurea versus switching to a sulfonylurea.

Table 4

Adverse events when adding or switching to sulfonylureas

Exposure	No of patients	No of events	Person years	Incidence rate (95% CI) per 1000 person years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Myocardial infarction						
Adding sulfonylureas	13 203	57	11 442	5.0 (3.8 to 6.5)	Reference	Reference
Switching to sulfonylureas	9759	68	5138	13.2 (10.4 to 16.8)	2.65 (1.86 to 3.78)	1.51 (1.03 to 2.24)
Ischaemic stroke						
Adding sulfonylureas	13 300	63	11 542	5.5 (4.3 to 7.0)	Reference	Reference
Switching to sulfonylureas	9771	46	5185	8.9 (6.6 to 11.8)	1.60 (1.09 to 2.34)	0.88 (0.58 to 1.33)
Cardiovascular death						
Adding sulfonylureas	13 217	75	11 464	6.5 (5.2 to 8.2)	Reference	Reference
Switching to sulfonylureas	9779	93	5204	17.9 (14.6 to 21.9)	2.70 (1.99 to 3.66)	1.22 (0.87 to 1.71)
All cause mortality						
Adding sulfonylureas	13 242	217	11 504	18.9 (16.5 to 21.5)	Reference	Reference
Switching to sulfonylureas	9800	256	5216	49.1 (43.4 to 55.5)	2.57 (2.14 to 3.08)	1.23 (1.00 to 1.50)
Severe hypoglycaemia						
Adding sulfonylureas	13 215	39	11 440	3.4 (2.5 to 4.7)	Reference	Reference
Switching to sulfonylureas	9770	45	5177	8.7 (6.5 to 11.6)	2.61 (1.70 to 4.01)	1.06 (0.65 to 1.71)

*The models for myocardial infarction, ischaemic stroke, cardiovascular death, and severe hypoglycaemia were adjusted for age, sex, deciles of propensity score, history of the respective outcome in the year before cohort entry (or, for the case of cardiovascular death, history of myocardial infarction or ischaemic stroke), body mass index category, diuretics, statins, paracetamol, opioids, and nephropathy. The model for all cause mortality was adjusted for age, sex, deciles propensity score, body mass index category, diuretics, statins, paracetamol, opioids, and nephropathy.

Reprinted from "Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: Population based cohort study", by A. Douros, S. Dell'Aniello, O. Yu, K.B. Filion, L. Azoulay and S. Suissa, 2018, *BMJ, 362*, p. 8. Copyright 2018 by The BMJ.

Limitations to this study include a short duration of follow up and the fact that drug doses were not considered.

Maruthur et al. (2016) completed a systematic review comparing the safety and effectiveness of monotherapies and metformin-based combination therapies in adults with

T2DM. This review consisted of 204 studies with 81% of them being randomized controlled trials. The studies ranged from three months to eight years with the majority of the studies lasting less than two years. Participants were overweight or obese and had an A1c of 7-9%. Safety outcomes were assessed and Maruthur et al. established that sulfonylureas increased the risk of hypoglycemia as a monotherapy and as a metformin-based combination therapy. Sulfonylureas were associated with weight gain. Gastrointestinal side effects (nausea, vomiting, diarrhea) are associated with GLP-1s alone or in combination with metformin more than any other monotherapy or combination therapy.

Courtney, Nayar, Rajeswaran, and Jandhyala (2017) reported adverse effects of GLP-1s to include nausea, diarrhea, upper respiratory tract infections, injection site reactions, and hypoglycemia. Pancreatitis may be associated with the use of GLP-1s. Long term studies of the risk of pancreatitis in GLP-1 use have not necessarily indicated an increased risk, but it continues to be monitored.

DISCUSSION

The treatment of T2DM continues to evolve with the new discoveries in treatment with antidiabetic drugs. Each treatment plan is individualized to the patient's comorbidities and preferences and by weighing the benefits and risks. The next section is a discussion of the review of literature of GLP-1s and sulfonylureas as adjuvant therapy to metformin and it will highlight the benefits and risks of the therapy.

Despite T2DM being a complex disease, literature does agree on the first line of treatment to be diet and exercise. If diet and exercise alone are not enough to lower the A1c to acceptable levels, metformin is the first antidiabetic medication to initiate. If additional adjuvant

therapy is needed beyond metformin, there are several options which should be selected on an individual basis.

Chou et al. (2017), Courtney et al. (2017), and Maruthur et al. (2016) all report that the benefits of GLP-1s include decreasing cardiovascular risk factors of decreasing weight and blood pressure. Chou et al. and Courtney et al. highlight the cardiovascular benefits of GLP-1s. By decreasing the risk factors for cardiovascular events, fewer deaths from cardiovascular causes, nonfatal myocardial infarctions, and nonfatal strokes were reported.

Choby (2017) provides cost information in Table 3 above which supports the idea that sulfonylureas are more affordable than GLP-1s. Sulfonylureas can cost between $10-90 where as GLP-1s range from $500 to $769. The affordability of medication plays a role in selecting an antidiabetic drug for different patient populations.

Currently, sulfonylureas are available as oral medications as opposed to GLP-1s that are only available in the injectable form. Instead of only daily dosing with GLP-1s, there are options for once a week dosing as well. The route of administration may affect prescribing patterns depending on patient preference.

Gastrointestinal side effects are the most commonly reported adverse effects in those who use GLP-1s. Those side effects may include nausea, vomiting, and diarrhea. It is also recommended to avoid GLP-1s in anyone with a history of pancreatitis. Choby (2017), Maruthur et al. (2016) and Courtney et al. (2017) all report gastrointestinal side effects in the studies reviewed. Courtney et al. also adds an injection site reaction to the list of adverse effects for GLP-1s and Choby reports on the cost of GLP-1s being a negative effect.

Choby (2017) and Maruthur et al. (2016) stated hypoglycemia and weight gain as the most reported adverse effects of sulfonylureas. Douros et al. (2018) indicate an increased risk of myocardial infarction, all cause mortality, and severe hypoglycemia with sulfonylureas when compared to metformin monotherapy.

Maruthur et al. (2016) reported on three randomized controlled trials (n = 2,557) with an odds ratio of 3.4-7.1 and a risk difference of 15-30%. They found that the metformin and GLP-1 combination to be favored over metformin and sulfonylurea combination with a moderate strength of evidence in supporting effectiveness.

Overall, the review of literature demonstrates benefits of GLP-1s over sulfonylureas. The adverse effects with GLP-1s may decrease with length of treatment while adverse effects of sulfonylureas remain unchanged. The cost, gastrointestinal side effects, and the fact that the GLP-1s are currently only available in an injectable form may be a deterrent for patients.

APPLICABILITY TO CLINICAL PRACTICE

In clinical practice, T2DM is a diagnosis that is encountered almost daily in the primary care setting. If it is not in terms of direct treatment, it is seen as a comorbidity in the adult population. New treatment options continue to be developed to improve the management of adults with T2DM. Finding the appropriate treatment to manage diabetes can be a challenge. Between the dosage of medication, class of medication, adverse effects, and affordability of the medications, it may take multiple clinic visits to be obtain diabetic control before the possibility of the body changing and needing to find the necessary balance again. This can be very challenging for the provider and frustrating for the patient.

With this research, it was found that treatment with GLP-1s offer many benefits to T2DM such as weight loss, low risk of hypoglycemia, decrease in systolic blood pressure, and cardiovascular protective benefits. These benefits make this injectable medication more appealing. However, the gastrointestinal side effects are the largest drawback and potentially the biggest cause for discontinuation of this treatment. The cost and method of administration are also limitations for this antidiabetic medication for patients.

Sulfonylureas demonstrate solid evidence of their effectiveness in lowering A1c which strengthens the justification for their continued use as a second line treatment in adults with T2DM that are not controlled with metformin alone. Due to the established history, there has been adequate research supporting their use as an antidiabetic medication. The cost is significantly less for sulfonylureas as compared to GLP-1s. The option of a second line treatment being an oral form may be more appealing to some patients as compared to an injectable medication. Sulfonylureas are known to have the potential for weight gain as well as

hypoglycemia when utilized as a monotherapy and to a less extent as a combination therapy with metformin.

With the future of genetic research, the potential to predict the effectiveness or lack of effectiveness of different medications for patients may dramatically change the prescribing patterns for providers treating T2DM.

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