

Sulfonylurea Agents & Combination Products
Drug Class Review
68:20.20 Sulfonylureas

Chlorpropamide (Diabinese®)
Glimepiride (Amaryl®)
Glipizide (Glucotrol®; Glucotrol® XL)
Glyburide (Diabeta®; Glynase®)
Tolazamide (Tolinase®)
Tolbutamide (Orinase®)
Glipizide & Metformin (Metaglip™)
Glyburide & Metformin (Glucovance®)
Pioglitazone & Glimepiride (Duetact™)
Rosiglitazone & Glimepiride (Avandaryl®)

Final Report
July 2013

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Table of Contents

Executive Summary.....	3
Introduction	5
Table 1. Comparison of Sulfonylurea Agents.....	6
<i>Disease Overview</i>	8
Table 2. Comparison of Antidiabetes Agents	10
Pharmacology/Pharmacokinetics.....	12
Table 3. Pharmacokinetics of the Sulfonylurea Agents.....	12
Methods.....	13
Clinical Efficacy	13
Table 4. Mean HbA1c reduction in clinical trials	13
Adverse Drug Reactions.....	15
Summary.....	15
References	17
Evidence Table. Clinical Trials Evaluating the Sulfonylurea Agents.....	18

Executive Summary

Introduction: Six sulfonylurea agents are currently available for use in the United States: chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, and tolbutamide. All sulfonylurea agents are available as a generic, are administered orally and are indicated in the treatment of Type 2 diabetes mellitus. Glipizide is available as an immediate release tablet or extended release tablet and glyburide has a micronized formulation. Glipizide and glyburide are both available in combination with metformin and glimepiride is available in combination with each of the thiazolidinediones (pioglitazone and rosiglitazone).

Diabetes mellitus (DM) is a broad term describing metabolic disorders associated with hyperglycemia. An estimated 300 million people worldwide have DM and it is listed as the seventh leading cause of death. The prevalence of DM increases with age, is similar across genders, varies across different ethnic populations and continues to be a leading cause of morbidity and mortality across the world. Treatment of Type 2 diabetes may include a combination of antidiabetes agents in addition to therapies to treat other comorbid conditions associated with DM. The American Diabetes Association Standards of Medical Care in Diabetes (2013) recommends metformin as the preferred first-line agent for treatment of Type 2 diabetes. A sulfonylurea agent may be added to a patient's regimen if metformin monotherapy is contraindicated, not tolerated or does not achieve the target glycosylated hemoglobin (HbA1c) at 3-6 months. Choice of diabetes treatment should be based on individual patient characteristics.

Clinical Efficacy: The efficacy of the second-generation sulfonylurea agents is examined in four comparative clinical trials. The mean HbA1c reduction in clinical trials is comparable between agents. Based on the limited evidence, no difference in efficacy was demonstrated between second-generation sulfonylurea treatment groups. Two trials reported greater frequency of hypoglycemic events in glyburide treatment groups compared to glimepiride treatment groups but the differences were not statistically significant.

Adverse Drug Reactions: The sulfonylurea agents are well tolerated by adult patients with Type 2 diabetes. Hypoglycemia and weight gain are the two major adverse effects reported with sulfonylurea therapy. Hypoglycemia occurs more frequently with the sulfonylurea agents when used in combination with other diabetes therapies or in geriatric patients. Glyburide is the second-generation sulfonylurea most likely to accumulate in patients with reduced renal function and result in hypoglycemia. Sulfonylurea therapy may also be associated with hepatotoxicity, allergic reactions, and adverse cardiovascular outcomes. The initiation of all sulfonylurea agents should be at a low dose with careful titration to effect.

Summary: The sulfonylurea agents are indicated in the treatment of Type 2 diabetes mellitus and should be considered second-line or add-on therapy in patients when metformin monotherapy is contraindicated not tolerated or does not achieve the target HbA1c. The evidence suggests each of the second-generation sulfonylurea agents are efficacious in reducing HbA1c in patients with Type 2 diabetes. Hypoglycemia and weight gain are the most commonly reported adverse events with sulfonylurea treatment. In clinical trials, higher rates of hypoglycemic events were reported with glyburide treatment. Choice of antidiabetes therapy should be based on

individual patient characteristics, including: efficacy, cost, response to other diabetes therapies, potential adverse effects, comorbidities, risk of hypoglycemia, and patient preference.

Introduction

Several diabetes therapies are currently available for use in the United States including: sulfonylureas, biguanides, insulin, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides and incretin-based therapies (DPP-4 inhibitors and GLP-1 agonists).^{1,2} This review will focus on the sulfonylurea agents. Six medications are included in the sulfonylurea drug class: chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, and tolbutamide.^{3,4} All of the sulfonylurea agents are available as an oral tablet. Glipizide is available as an immediate release tablet or extended release tablet. Glyburide has a micronized formulation. Glipizide and glyburide are both available in combination with metformin and glimepiride is available in combination with pioglitazone and rosiglitazone. Dosing for each of the agents varies depending on the specific indication and individual patient characteristics. Table 1 provides a summary of the available agents.

Table 1. Comparison of Sulfonylurea Agents¹⁻⁴

Product	Drug class	Available strengths (mg)	Labeled uses	Dose range, Adults	Dose titration	Generic available
Chlorpropamide (Diabinese®)	First-generation sulfonylurea	100, 200	Management blood sugar in Type 2 diabetes mellitus as an adjunct to diet and exercise	<u>Adult</u> : 250 mg daily <u>Geriatric</u> : 100-125 mg daily <u>Renal impairment</u> : avoid use in pts with Clcr<50. In Pts Clcr is >50 reduce by 50% <u>Hepatic impairment</u> : reduced initial dose	<u>Adult</u> : at 5-7d increase 50-125 mg at 3-5 d intervals as needed <u>Geriatric</u> : see adult, may require slower up titration	Yes
Glimepiride (Amaryl®)	Second-generation sulfonylurea	1, 2, 4	Management of Type 2 diabetes mellitus as an adjunct to diet and exercise	<u>Adult</u> : 1-2 mg daily <u>Geriatric</u> : 1 mg daily <u>Renal impairment</u> : 1 mg daily <u>Hepatic impairment</u> : no adjustment needed in minor. Severe impairment use is contraindicated	<u>Adult</u> : 1-2 mg every 1-2 weeks as needed <u>Geriatric</u> : conservative titration <u>Renal</u> : conservative titration	Yes
Glipizide (Glucotrol®; Glucotrol® XL)	Second-generation sulfonylurea	<u>Immediate release</u> : 5, 10 <u>Extended release</u> : 2.5, 5, 10	Management of Type 2 diabetes mellitus as an adjunct to diet and exercise	<u>Adult</u> : 5mg daily <u>Geriatric</u> : 2.5 mg daily <u>Renal impairment</u> : No adjustment listed in labeling <u>Hepatic Impairment</u> : 2.5 mg daily	<u>Adult IR</u> : 2.5-5 mg as frequently as every few days <u>Adult ER</u> : adjustments no more frequently than every 7 days <u>Geriatric IR</u> : 2.5-5 mg every 1-2 weeks as needed <u>Geriatric ER</u> : Conservative titration	Yes
Glyburide (Diabeta®; Glynase®)	Second-generation sulfonylurea	<u>Tablet (mg)</u> : 1.25, 2.5, 5 <u>Micronized tablet (mg)</u> : 1.25, 2.5, 5	Adjunct to diet and exercise for the management of Type 2 diabetes	<u>Adult</u> : 2.5-5 mg daily <u>Adult Micro</u> : 1.5-3 mg daily <u>Geriatric</u> : 1.25-2.5 mg daily <u>Renal Impairment</u> : not recommended in Clcr <50 <u>Hepatic</u> : avoid in severe disease	<u>Adult</u> : no more than 2.5 mg/day at weekly intervals <u>Adult Micro</u> : no more than 1.5 mg/day at weekly intervals <u>Geriatric</u> : 1.25-2.5 mg every 1-3 weeks	Yes
Tolazamide (Tolinase®)	First-generation sulfonylurea	250, 500	Adjunct to diet for the management of mild-to-moderately severe, stable, Type 2 diabetes mellitus	<u>Adult FBG<200</u> : 100 mg daily <u>Adult FBG>200</u> : 250 mg daily <u>Geriatric</u> : see adult <u>Renal impairment</u> : Conservative initial treatment <u>Hepatic</u> : Conservative initial treatment	<u>Adult</u> : 100-250 mg/day at weekly intervals <u>Geriatric</u> : see adult	Yes

Tolbutamide (Orinase®)	First-generation sulfonylurea	500	Adjunct to diet for the management of Type 2 diabetes	<u>Adult:</u> 1-2 g daily <u>Geriatric:</u> 250 mg 1-3 times a day <u>Renal Impairment:</u> No adjustment <u>Hepatic Impairment:</u> No adjustment	N/A	Yes
Glipizide and Metformin (Metaglip™)	Sulfonylurea and biguanide combination agent	2.5/250 2.5/500 5/500	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus (noninsulin dependent, NIDDM)	See recommendations for individual agents 2.5-10/250-2000	See recommendations for individual agents	Yes
Glyburide and Metformin (Glucovance®)	Sulfonylurea and biguanide combination agent	1.25/250 2.5/500 5/500	Adjunct to diet and exercise for the management of Type 2 diabetes mellitus (noninsulin dependent, NIDDM)	See recommendations for individual agents 1.25/250-20/2000	See recommendations for individual agents	Yes
Pioglitazone and Glimepiride (Duetact™)	Sulfonylurea and thiazolidinedione combination agent	30/2 30/4	Management of Type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise in patients already treated with a thiazolidinedione and a sulfonylurea or who have inadequate control on either agent alone	See recommendations for individual agents 30/2-4	See recommendations for individual agents	Yes
Rosiglitazone and Glimepiride (Avandaryl®)	Sulfonylurea and thiazolidinedione combination agent	4/1 4/2 4/4 8/2 8/4	Management of Type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise	See recommendations for individual agents 4/1-8/4	See recommendations for individual agents	No

Key: IR = immediate release, ER = extended release, N/A = information not available

Disease Overview

Diabetes mellitus (DM) is a broad term describing metabolic disorders associated with hyperglycemia.^{1,2} In 2010, an estimated 300 million people worldwide had DM compared to 30 million cases in 1985. This number is expected to continue to rise and the International Diabetes Federation estimates 438 million individuals will have diabetes by the year 2030. In the United States (US), the Centers for Disease Control and Prevention (CDC) estimated over 25 million people had diabetes in 2010 (~8.3% of the population) and it was the seventh leading cause of death in 2007. DM is also the leading cause of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, blindness, and cardiovascular diseases in the US. A recent study suggests diabetes is the fifth leading cause of death worldwide and is responsible for almost 4 million deaths in 2010. The prevalence of DM increases with age, is similar across genders, varies across different ethnic populations and will continue to be a leading cause of morbidity and mortality across the world.^{1,2}

Diabetes mellitus is a metabolic disorder associated with hyperglycemia as a result of insulin deficiency, reduced insulin secretion, and/or increased glucose production.^{1,2} DM is classified as Type 1 and Type 2 based on the pathogenic process leading to hyperglycemia. Both Types are associated with a complex combination of genetics and environmental factors and begin with abnormal glucose homeostasis. A severe or total insulin deficiency occurs in Type 1 DM. In Type 2 DM, varying degrees of insulin resistance, impaired insulin secretion, and increased glucose production follows the initial glucose imbalance. The defects in insulin action in Type 2 diabetes provide important potential therapeutic implications and pharmacologic agents are available to target these specific metabolic disorders. DM may cause secondary pathophysiologic changes in many organ systems including the renal, neurological, cardiovascular and ocular systems. Diabetes mellitus is a chronic disease which places a huge burden on both the patient and on the health care system as a whole.^{1,2}

Treatment of DM varies depending on the clinical subset of DM present and individual patient characteristics.^{1,2,5} For Type 2 diabetes, treatment may include a combination of the agents indicated in treating DM in the United States (sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides and incretin-based therapies) in addition to therapies to treat other comorbid conditions associated with DM (ACE inhibitors, HMG-CoA reductase inhibitors (statins), low-dose aspirin, etc.). The two main goals of DM treatment are to eliminate symptoms and reduce microvascular and macrovascular complications associated with chronic hyperglycemia. The American Diabetes Association Standards of Medical Care in Diabetes (2013)⁶ recommends metformin as the preferred first-line agent for treatment of Type 2 diabetes. In patients with significantly elevated blood glucose levels or HbA1c level, insulin therapy may be the preferred first-line agent. If metformin monotherapy is contraindicated, not tolerated or does not effectively achieve the target glycosylated hemoglobin (HbA1c) at 3-6 months, a second agent (sulfonylurea, thiazolidinedione, incretin-based therapy or insulin) may be used or added. Choice of pharmacological agents should be based on individual patient characteristics, including: efficacy, cost, potential adverse effects, comorbidities, risk of hypoglycemia, and patient preference.^{1,2,5} Table 2 compares the available diabetes therapies.

The sulfonylurea agents are the oldest class of oral anti-diabetes therapies and are currently used as second-line or add-on treatment options for Type 2 diabetes.⁶ The agents stimulate pancreatic beta-cells to produce insulin, increase cellular uptake and utilization of glucose, and decrease glucose production in the liver.^{1, 2, 5} Six agents are currently available in the US, all as oral tablets. The sulfonylureas may be divided into two groups: first-generation agents (chlorpropamide, tolazamide, tolbutamide) and second-generation agents (glimepiride, glipizide, glyburide). The first generation agents have longer half-lives, increased incidence of hypoglycemia, and more drug interactions. The second generation agents have quicker onsets of action, shorter half-lives, and lower incidence of hypoglycemia. Glipizide is available in both immediate release and extended release formulations. Many of the agents are available in combination with other anti-diabetes therapies. See Table 1 for a comparison of all the available agents. The therapeutic effects of the sulfonylurea agents can result in hypoglycemia. Slow initiation and titration of the agents is recommended. The sulfonylurea agents are not used in patients with Type 1 diabetes whose pancreas is unable to produce insulin.

Table 2. Comparison of Antidiabetes Agents^{1-4, 7-9}

Class	Agents in class	Route of administration	Mechanism of action	Labeled Indications
Alpha-glucosidase Inhibitors	Acarbose Miglitol	Oral tablets	Competitive inhibitor of pancreatic enzymes, resulting in delayed metabolism of starches and some sugars	Adjunct to diet and exercise to lower blood glucose in patients with Type 2 diabetes mellitus
Amylin Mimetics	Pramlintide	Injectable solution; subcutaneous	Synthetic analog of human amylin which works by prolonging gastric emptying, reduces postprandial glucagon secretion, and centrally-mediate appetite suppression	Adjunctive treatment with mealtime insulin in Type 1 diabetes mellitus Adjunctive treatment with mealtime insulin in Type 2 diabetes mellitus, with or without concurrent sulfonylurea and/or metformin
Biguanides	Metformin Metformin/Alogliptin Metformin/Glipizide Metformin/Glyburide Metformin/Linagliptin Metformin/Pioglitazone Metformin/Repaglinide Metformin/Rosiglitazone Metformin/Saxagliptin Metformin/Sitagliptin	Oral tablets	Decreases hepatic glucose production, decreasing intestinal absorption of glucose and improving insulin sensitivity	First-line management of Type 2 diabetes mellitus <u>Unlabeled Indications:</u> Gestational diabetes mellitus (GDM); polycystic ovary syndrome (PCOS); prevention of Type 2 diabetes mellitus
Dipeptidyl peptidase IV (DPP-IV) Inhibitors	Alogliptin Alogliptin/Metformin Alogliptin/Pioglitazone Linagliptin Linagliptin/Metformin Saxagliptin Saxagliptin/Metformin Sitagliptin Sitagliptin/Metformin Sitagliptin/Simvastatin	Oral tablets	Inhibits dipeptidyl peptidase IV (DPP-IV) enzyme resulting in prolonged active incretin levels resulting in increased insulin synthesis & release and decreased glucagon secretion	Management of Type 2 diabetes mellitus as an adjunct to diet and exercise as monotherapy or in combination with other antidiabetic agents
Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists	Exenatide Liraglutide	Injectable solution; subcutaneous	Analogues of the hormone incretin which increase glucose-dependent insulin secretion, decrease inappropriate glucagon secretion, increase B-cell growth/replication, slow gastric emptying, and decrease food intake	Treatment of Type 2 diabetes mellitus *May also improve hypertension in patients with diabetes

<u>Insulins</u>	<p><u>Rapid-acting</u> Aspart: Novolog Gulisine: Apidra Lispro: Humalog</p> <p><u>Short-acting</u> Regular: Humulin, Humulin R, Novolin</p> <p><u>Intermediate-acting</u> NPH: Humulin N, Novolin N</p> <p><u>Intermediate to Long-acting</u> Detemir</p> <p><u>Long-acting</u> Glargine</p> <p><u>Combination Products</u> Aspart protamine + Aspart Lispro protamine + Lispro NPH + Regular: Humulin 70/30, Novolin 70/30</p>	Injectable solution; subcutaneous, intravenous	Insulin acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrate, protein, and fats. Target organs for insulin include the liver, skeletal muscle, and adipose tissue	Treatment of Type 1 diabetes mellitus and Type 2 diabetes mellitus to improve glycemic control
Meglitinides	Nateglinide Repaglinide Repaglinide/Metformin	Oral tablets	Phenylalanine derivatives which stimulate insulin release and reduce postprandial hyperglycemia	Management of Type 2 diabetes mellitus as monotherapy or in combination with metformin or a thiazolidinedione
Sulfonylureas	Chlorpropamide Glimepiride Glimepiride/Pioglitazone Glimepiride/Rosiglitazone Glipizide Glipizide/Metformin Glyburide Glyburide/Metformin Tolazamide Tolbutamide	Oral tablets	Stimulates insulin release, reduces glucose output and increases insulin sensitivity	Management of Type 2 diabetes mellitus as monotherapy or in combination with metformin or insulin
Thiazolidinediones	Pioglitazone Pioglitazone/Alogliptin Pioglitazone/Glimepiride Pioglitazone/Metformin Rosiglitazone Rosiglitazone/Glimepiride Rosiglitazone/Metformin	Oral tablets	Agonists for peroxisome proliferator-activated receptor-gamma (PPARgamma) which influences the production of a number of gene products involved in glucose and lipid metabolism	Management of Type 2 diabetes mellitus as monotherapy or in combination with a sulfonylurea, metformin, or sulfonylurea plus metformin

Pharmacology/Pharmacokinetics

The sulfonylurea agents act on the beta-cells of the pancreas by binding to the atp-dependent potassium channel causing a chain of events that lead to increased secretion of insulin. The sulfonylurea agents may also slow the clearance of insulin. These elevated insulin levels are only seen with acute exposure to the medication. Insulin levels return to the same levels as those before exposure when the sulfonylureas are used long term. Despite the lower insulin levels the glucose levels remain lower. The mechanism for this is unknown.⁴

The sulfonylurea agents are absorbed well from the GI tract. Decreased absorption occurs when taken with food. Glyburide has a micronized formulation which provides better bioavailability and allows for lower dosing. Once absorbed, the agents are highly protein bound. The sulfonylurea agents have short half-lives but the glucose lowering effects are long lasting and enable once a day dosing. The sulfonylurea agents are metabolized in the liver and are primarily excreted by the kidneys.⁴ Glyburide has a weakly active metabolite which is eliminated renally and may accumulate in patients with reduced renal function (i.e. geriatric patients). Table 3 summarizes the pharmacokinetic properties of the individual agents.²

Table 3. Pharmacokinetics of the Sulfonylurea Agents^{3,4}

Product	Onset	Peak	T1/2 plasma	Metabolism	Metabolites
Chlorpropamide	1h	<u>Effect:</u> 3-6h <u>Serum:</u> 2-4h	36h 50-200h in ESRD	80% Hepatic, primary CYP2C9	No active metabolites listed
Glimepiride	2-3h	<u>Serum:</u> 2-3h	5-9h	Hepatic CYP2C9	M1 metabolite: 33% activity M2 metabolite: inactive
Glipizide		<u>Serum:</u> IR 1-3 h ER 6-12h	2-5h	Hepatic CYP2C9	Inactive
Glyburide	15-60m	<u>Serum:</u> 2-4h	10h; 4h for micronized	Hepatic CYP2C9	Weak activity *eliminated renally and may accumulate in geriatric patients
Tolazamide	20m	<u>Effect:</u> 4-6h <u>Serum:</u> 3-4h	7h	Hepatic, exact mechanism unknown	5 metabolites: activity 0-70%
Tolbutamide	1h	<u>Serum:</u> 3-4h	4-25h	Hepatic CYP2C9	2 metabolites: mild to inactive

Key: IR = immediate release, ER = extended release, ESRD = end stage renal disease, N/A = information not available

Methods

A literature search was conducted to identify articles addressing the efficacy of the sulfonylurea agents, searching the MEDLINE database (1950 – 2012), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE during the preceding 20 years, evaluating efficacy of the sulfonylurea agents with reduction of symptoms or cure as the endpoint are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials evaluating outcomes not related to efficacy or trials comparing monotherapy with combination regimens are excluded.

Clinical Efficacy

The efficacy of sulfonylurea agents is not directly compared in any meta-analyses or systematic reviews. Comparative efficacy is examined in four clinical trials.¹⁰⁻¹⁴ These clinical trials compare second-generation sulfonylureas only. Gliclazide is evaluated in two clinical trials; however, gliclazide is not available in the United States. Some comparative studies reviewing first-generation sulfonylureas and combination agents are available but the quality of evidence is lacking.^{15, 16} The relative HbA1c reductions are listed in Table 4. The mean HbA1c reduction in clinical trials is comparable between agents.

Table 4. Mean HbA1c reduction in clinical trials

Agents	Mean HbA1c Reductions
Glimepiride (Amaryl®)	0.85 to 1.0
Glipizide (Glucotrol®; Glucotrol® XL)	0.95
Glyburide (Diabeta®; Glynase®)	0.85 to 1.27

Kitabchi et al¹² compared glyburide to glipizide in a small trial of 18 patients with Type 2 diabetes over a fifteen month period. During the initial 2 months prior to randomization all patients were withdrawn from their oral anti-diabetic treatment or insulin therapy. The glipizide dosage was started at 5 mg once daily and increased by 2.5 to 5 mg every 14 days up to 20 mg as needed for glucose control. Glyburide dosage was started at 2.5 mg to 5 mg once daily and increased by 2.5 mg every 7 days up to 20 mg as needed for glucose control. No significant difference in reduction of HbA1c, fasting plasma glucose, or post-prandial glucose was found between treatment groups at 15 months. The rate of hypoglycemia was similar between both groups with 101 episodes in the glipizide treatment group (n=9) and 110 episodes in the glyburide treatment group (n=9). Overall, glipizide and glyburide treatments were equally efficacious in lowering HbA1c, fasting plasma glucose, and postprandial glucose levels compared to baseline in patients with Type 2 diabetes.

Birkeland et al¹³ also compared glyburide to glipizide treatment. Forty-six patients with Type 2 diabetes were followed over a fifteen month period. Glyburide 2.5 mg once daily, glipizide 2.5 mg once daily, and placebo were compared. Dose was titrated in both active treatment groups until fasting plasma glucose and HbA1c goals were reached. At three months, both sulfonylurea groups had similar rates of HbA1c reduction. However, from three to fifteen months a steady increase in HbA1c was seen in all groups ($p < 0.001$). Fasting plasma glucose was significantly lower compared to baseline in both treatment groups at month three ($p < 0.05$) and only in the glipizide treatment group at month fifteen ($p < 0.05$). Two patients in the glyburide group withdrew in the first week due to hypoglycemia but the rate of hypoglycemic events over the entire study period was not reported. Overall, no significant differences in efficacy were reported between glyburide and glipizide treatment groups and outcomes were similar to the placebo treatment group.

Draeger et al¹⁴ compared glyburide to glimepiride treatment in 1,044 patients with Type 2 diabetes over a 12 month period. Glyburide doses started at 2.5 mg once daily and were increased as needed, to achieve optimal glucose control, up to 20 mg once daily. Glimepiride doses started at 1 mg once daily and increased as needed to 8 mg once daily. No significant difference in HbA1c was found between glyburide treatment (8.4%) and glimepiride treatment (8.3%) at 12 months. No significant difference in fasting plasma glucose was found between glyburide treatment (174 mg/dL) and glimepiride treatment (168 mg/dL). Hypoglycemic events were reported more frequently in the glimepiride treatment group (105) compared to the glyburide treatment group (150). Glyburide and glimepiride were found to be equivalent in glycemic control over a 12 month period. However, glimepiride was associated with fewer hyperglycemic events compared to glyburide.

Dills et al¹⁷ compared glyburide and glimepiride treatment in 577 patients with Type 2 diabetes over a 12 month period. Glyburide doses ranged from 1.25 mg to 20 mg once daily. Glimepiride doses ranged from 1 mg to 16 mg once daily. No significant difference in HbA1c reduction was found between glyburide treatment ($0.83 \pm 0.96\%$) and glimepiride treatment ($0.85 \pm 1.12\%$) from baseline to 12 months. No significant difference in fasting plasma glucose reduction was found between glyburide treatment (44 ± 60 mg/dL) and glimepiride treatment (49 ± 54 mg/dL) from baseline to 12 months. The rate of hypoglycemic events was not significantly different between glyburide treatment (48 patients or 17%) and glimepiride treatment (34 patients or 12%) over the 12 months of the study. Overall, safety and efficacy outcomes were similar between treatment groups.

Based on the limited evidence available evaluating the second generation sulfonylurea agents, no difference in safety and efficacy was demonstrated between treatment groups. Two trials reported greater frequency of hypoglycemic events in glyburide treatment groups compared to glimepiride treatment groups but the differences were not statistically significant. Overall, glyburide, glimepiride, and glipizide appear to be equally safe and efficacious in the treatment of Type 2 diabetes.

Adverse Drug Reactions

In general, the sulfonylurea agents are well tolerated by adult patients with Type 2 diabetes. Hypoglycemia and weight gain are the two major adverse effects reported with sulfonylurea therapy.¹⁸ Hypoglycemic events may occur more frequently when administered with other diabetes therapies, as is the case with sulfonylurea/thiazolidinedione combination products (Duetact™ and Avandaryl®). Hypoglycemic events may also be more serious in geriatric patients, as this population has a higher frequency of hypoglycemic unawareness, falls and cognitive dysfunction.¹⁸⁻²⁰ Glyburide is the second-generation sulfonylurea most likely to accumulate in patients with reduced renal function, resulting in hypoglycemia, and is not recommended in patients with a creatinine clearance less than 50 mL/min. The initiation of all sulfonylurea agents should be at a low dose with careful titration to effect.²⁰

The sulfonylurea agents may also be associated with hepatotoxicity, allergic reactions, and cardiovascular outcomes. First-generation agents, chlorpropamide and tolbutamide, have the highest frequency of hepatotoxicity.²¹ Drug-induced hepatotoxicity with second-generation sulfonylureas is rare. Sulfonylurea agents have a sulfa-like structure and allergic reactions are possible. In patients known to have an allergy to a sulfa-containing product a 17% cross-reactivity is possible.^{3,4} A disulfuram-reaction is possible with any of the sulfonylurea agents but is most frequent with chlorpropamide. In addition, a recent study evaluating cardiovascular outcomes associated with long term diabetes therapy suggests sulfonylurea use may be associated with an increased risk of acute myocardial infarction, stroke or death.²² More studies are required to determine the actual risk and if there are any differences between the individual sulfonylurea agents.

Summary

Diabetes mellitus (DM) is broad term describing metabolic disorders associated with hyperglycemia. Treatment of DM varies depending on the clinical subset of DM present and individual patient characteristics and may include a combination of antidiabetes agents in addition to therapies to treat other comorbid conditions associated with DM. The American Diabetes Association Standards of Medical Care in Diabetes (2013) recommends metformin as the preferred first-line agent for treatment of Type 2 diabetes. A sulfonylurea may be added to a patients regimen if metformin monotherapy is contraindicated, not tolerated or does not achieve the target HbA1c at 3-6 months. Six sulfonylurea agents are currently available for use in the United States: chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, and tolbutamide.

Comparative clinical efficacy is only available for the second-generation sulfonylurea agents. Overall, limited clinical evidence is available and only four clinical trials were identified for evaluation. Based on the limited evidence, no difference in efficacy was demonstrated between second-generation sulfonylurea treatment groups. Two trials reported greater frequency of hypoglycemic events in glyburide treatment

groups compared to glimepiride treatment groups but the differences were not statistically significant. Hypoglycemia and weight gain are the most frequent adverse effects reported with sulfonylurea therapy and hypoglycemia may occur more frequently when administered with other diabetes therapies or in geriatric patients. Hepatotoxicity, allergic reactions, and adverse cardiovascular outcomes may also be associated with sulfonylurea therapy. Overall ranges of HbA1c reduction seen with glimepiride, glipizide and glyburide treatment in current literature are similar and choice of antidiabetes therapy should be based on individual patient characteristics, including: efficacy, cost, potential adverse effects, comorbidities, risk of hypoglycemia, and patient preference.

References

1. Powers AC. Chapter 344. Diabetes Mellitus. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012.
2. Powers AC, D'Alessio D. Chapter 43. Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus and Hypoglycemia. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York, NY: McGraw-Hill; 2011.
3. AHFS Drug Information, ed *AHFS 2013 Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists; 2013.
4. Lexi-Comp I, ed *Drug Information Handbook*. 21st ed. Hudson, OH: Lexi-Comp; 2013.
5. Nolte-Kennedy MS. Chapter 41. Pancreatic Hormones & Antidiabetic Drugs. In: Katzung BG, Masters SB, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 12th ed. New York, NY: McGraw-Hill; 2012.
6. Standards of medical care in diabetes--2013. *Diabetes Care*. Jan;36 Suppl 1:S11-66.
7. Amylin. Bydureon (exenatide extended-release) injectable suspension [package insert]San Diego, CA: Amylin Pharmaceuticals, Inc; 2012.
8. NovoNordisk. Victoza (liraglutide - rDNA origin) injection solution [package insert]Plainsboro, NJ: Novo Nordisk A/S; 2013.
9. Amylin. Byetta (exenatide) injection solution [package insert]San Diego, CA: Amylin Pharmaceuticals, Inc; 2011.
10. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in Type 2 diabetic patients. *European journal of clinical investigation*. Aug 2004;34(8):535-542.
11. Tessier D, Dawson K, Tetrault JP, Bravo G, Meneilly GS. Glibenclamide vs gliclazide in Type 2 diabetes of the elderly. *Diabetic medicine : a journal of the British Diabetic Association*. Dec 1994;11(10):974-980.
12. Kitabchi AE, Kaminska E, Fisher JN, et al. Comparative efficacy and potency of long-term therapy with glipizide or glyburide in patients with Type 2 diabetes mellitus. *The American journal of the medical sciences*. Mar 2000;319(3):143-148.
13. Birkeland KI, Furuseth K, Melander A, Mowinkel P, Vaaler S. Long-term randomized placebo-controlled double-blind therapeutic comparison of glipizide and glyburide. Glycemic control and insulin secretion during 15 months. *Diabetes care*. Jan 1994;17(1):45-49.
14. Draeger KE, Wernicke-Panten K, Lomp HJ, Schuler E, Roskamp R. Long-term treatment of Type 2 diabetic patients with the new oral antidiabetic agent glimepiride (Amaryl): a double-blind comparison with glibenclamide. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*. Sep 1996;28(9):419-425.
15. Sherwood G, Bressler R. Comparison of chlorpropamide with tolazamide in the treatment of diabetes mellitus. *Current therapeutic research, clinical and experimental*. Aug 1968;10(8):399-405.
16. Grinnell EH, Skillman TG, Brooks AM, Jr. A clinical pharmacologic comparison of glyhexamide, tolbutamide and chlorpropamide in the treatment of stable diabetes. *The American journal of the medical sciences*. Mar 1967;253(3):312-320.
17. Dills DG, Schneider J. Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study. Glimepiride/Glyburide Research Group. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*. Sep 1996;28(9):426-429.
18. Sakharova OV, Inzucchi SE. Treatment of diabetes in the elderly. Addressing its complexities in this high-risk group. *Postgrad Med*. Nov 2005;118(5):19-26, 29.
19. Silverberg AB, Ligaray KP. Oral diabetic medications and the geriatric patient. *Clin Geriatr Med*. Aug 2008;24(3):541-549, viii.
20. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med*. Aug 11-25 1997;157(15):1681-1686.
21. Nakao NL, Gelb AM, Stenger RJ, Siegel JH. A case of chronic liver disease due to tolazamide. *Gastroenterology*. Jul 1985;89(1):192-195.
22. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in Type 2 diabetes mellitus: a cohort study. *Ann Intern Med*. Nov 6;157(9):601-610.

Evidence Table. Clinical Trials Evaluating the Sulfonylurea Agents

Reference/Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects
				Results	Change from baseline	
Gliclazide versus Glimepiride						
Schernthaner et al, 2004 ¹⁰ Randomized, controlled trial	845	Patients > 35 years with Type 2 diabetes, treated for at least 3 months with diet alone or in combination with metformin or an α -glycosidase inhibitor, HbA1c 6.9% to 11.5%	Gliclazide modified release 30 mg, 60 mg, 90 mg, or 120 mg Glimepiride 1 mg, 2 mg, 3 mg, 4 mg, or 6 mg	Gliclazide = Glimepiride	Change in HbA1c level Gliclazide = Glimepiride Fasting plasma glucose Gliclazide = Glimepiride	Hypoglycemia Gliclazide: 22 (3.7%) Glimepiride: 56 (8.4%)
Gliclazide versus Glyburide						
Tessier et al, 1994 ¹¹ Randomized controlled trial	22	Elderly Patients with Type 2 diabetes	Glyburide Gliclazide	Gliclazide = Glyburide	Change in HbA1c level Gliclazide = Glyburide	Hypoglycemia Gliclazide: 4 Glyburide: 17
Glyburide versus Glipizide						
Kitabchi et al, 2000 ¹² Randomized, controlled trial	18	Patients with Type 2 diabetes, age 40-70, weight 110-200% of ideal body weight, Diastolic BP < 100 mmHg	Glyburide 2.5 to 20 mg Glipizide 5 mg to 20 mg	Glyburide = Glipizide	Change in HbA1c level Glyburide = Glipizide	Hypoglycemia Glyburide: 101 occurrences Glipizide: 110 occurrences
Birkeland et al, 1994 ¹³ Randomized, controlled trial	46	Patients with Type 2 diabetes, age 52 to 66, BMI 22.5 to 30.3	Glyburide 2.5 mg Glipizide 2.5 mg Placebo	Glyburide = Glipizide	Change in HbA1c level Glyburide = Glipizide Fasting glucose level Glyburide = Glipizide Post prandial glucose lowering Glyburide > Glipizide > Placebo	Not reported

Reference/Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects
				Results	Change from baseline	
Glyburide versus Glimepiride						
Draeger et al, 1996 ¹⁴ Randomized, controlled trial	1,044	Patients with Type 2 diabetes, on stable dose of glyburide	Glyburide 2.5 mg (up to 20 mg) Glimepiride 1 mg (increased up to 8 mg)	Glyburide = Glimepiride	Change in HbA1c level Glyburide = Glimepiride Fasting glucose level Glyburide = Glimepiride	Hypoglycemia Glyburide: 150 (29 %) Glimepiride: 105 (20 %)
Dills et al, 1996 ¹⁷ Randomized, controlled trial	577	Patients with Type 2 diabetes previously treated with sulfonylureas or diet alone, age 30 to 80	Glyburide 1.25 to 20 mg Glimepiride 1 to 16 mg	Glyburide = Glimepiride	Change in HbA1c level Glyburide = Glimepiride Fasting glucose level Glyburide = Glimepiride	Hypoglycemia Glyburide: 48 (17%) Glimepiride: 34 (12%)