PROGRAM PROFILE

Reducing or Discontinuing Insulin or Sulfonylurea When Initiating a Glucagon-like Peptide-1 Agonist

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Background: Hypoglycemia and weight gain are well-known adverse effects of insulin and sulfonylureas in patients with type 2 diabetes. Glucagon-like peptide-1 (GLP-1) agonist monotherapy has a low incidence of hypoglycemia, but when combined with insulin or sulfonylureas, patients have higher rates of hypoglycemia.

Methods: The primary study outcome was to determine the percentage of patients with dose reductions or discontinuation of insulin or a sulfonylurea at baseline, 3, 6, and 12 months. Secondary outcomes included changes in hemoglobin A_{1c} and body weight measured. This was a single-center, quality assurance, quality improvement, retrospective chart review of patients prescribed a GLP-1 agonist while on insulin and/or a sulfonylurea between January 1, 2019, and September 30, 2022, at a pharmacist-led patient aligned care team (PACT) clinic at the Wilkes-Barre Veterans Affairs Medical Center.

Results: This retrospective chart review included 136 patients. Throughout 12 months of following the pharmacist-led PACT clinic, 55 patients (57.3%) had ≥ 1 insulin dose reduction, 16 patients (29.6%) had ≥ 1 dose reduction of a sulfonylurea, 14 patients (14.6%) discontinued insulin, and 21 patients (38.9%) discontinued their sulfonylurea.

Conclusions: Patients taking insulin and/or sulfonylurea in combination with a GLP-1 agonist may require a dose reduction or discontinuation of the diabetic agents. Patients on both insulin and sulfonylurea may need closer monitoring due to the higher incidences of discontinuations compared with patients on only 1 of these agents. Dose reductions or discontinuations of these diabetic agents can promote positive patient outcomes, such as preventing hypoglycemia, minimizing weight gain, increasing weight loss, and reducing hemoglobin A_{1c}.

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Fed Pract. 2024;41(2). Published online February 14. doi:10.12788/fp.0452

Hypoglycemia and weight gain are well-known adverse effects that can result from insulin and sulfonylureas in patients with type 2 diabetes mellitus (T2DM).[1,2] Insulin and sulfonylurea medications can cause additional weight gain in patients who are overweight or obese, which can increase the burden of diabetes therapy with added medications, raise the risk of hypoglycemia complications, and raise atherosclerotic cardiovascular disease risk factors.[3] Although increasing the insulin or sulfonylurea dose is an option health care practitioners or pharmacists have, this approach can increase the risk of hypoglycemia, especially in older adults, such as the veteran population, which could lead to complications, such as falls.[2]

Previous studies focusing on hypoglycemic events in patients with T2DM showed that glucagon-like peptide-1 (GLP-1) agonist monotherapy has a low incidence of a hypoglycemic events. However, when a GLP-1 agonist is combined with insulin or sulfonylureas, patients have an increased chance of a hypoglycemic event.[3-8] According to the prescribing information for semaglutide, 1.6% to 3.8% of patients on a GLP-1 agonist monotherapy reported a documented symptomatic hypoglycemic event (blood glucose ≤ 70 mg/dL), based on semaglutide dosing.[9] Patients on combination therapy of a GLP-1 agonist and basal insulin and a GLP-1 agonist and a sulfonylurea reported a documented symptomatic hypoglycemic event ranging from 16.7% to 29.8% and 17.3% to 24.4%, respectively.[9] The incidences of hypoglycemia thus dramatically increase with combination therapy of a GLP-1 agonist plus insulin or a sulfonylurea.

When adding a GLP-1 agonist to insulin or a sulfonylurea, clinicians must be mindful of the increased risk of hypoglycemia. Per the warnings and precautions in the prescribing information of GLP-1 agonists, concomitant use with insulin or a sulfonylurea may increase the risk of hypoglycemia, and reducing the dose of insulin or a sulfonylurea may be necessary.[9-11] According to the American College of Cardiology guidelines, when starting a GLP-1 agonist, the insulin dose should be decreased by about 20% in patients with a well-controlled hemoglobin A_{1c} (HbA_{1c}).[12]

This study aimed to determine the percentage of patients who required dose reductions or discontinuations of insulin and sulfonylureas with the addition of a GLP-1 agonist. Understanding necessary dose re-

ductions or discontinuations of these concomitant diabetes agents can assist pharmacists in preventing hypoglycemia and minimizing weight gain.

METHODS

This clinical review was a single-center, retrospective chart review of patients prescribed a GLP-1 agonist while on insulin or a sulfonylurea between January 1, 2019, and September 30, 2022, at the Wilkes-Barre Veterans Affairs Medical Center (WBVAMC) in Pennsylvania and managed in a pharmacist-led patient aligned care team (PACT) clinic. It was determined by the US Department of Veterans Affairs Office of Research and Development that an institutional review board or other review committee approval was not needed for this nonresearch Veterans Health Administration quality assurance and improvement project. Patients aged ≥ 18 years were included in this study. Patients were excluded if they were not on insulin or a sulfonylurea when starting a GLP-1 agonist, started a GLP-1 agonist outside of the retrospective chart review dates, or were prescribed a GLP-1 agonist by anyone other than a pharmacist in their PACT clinic. This included if a GLP-1 agonist was prescribed by a primary care physician, endocrinologist, or someone outside the VA system.

The primary study outcomes were to determine the percentage of patients with a dose reduction of insulin or sulfonylurea and discontinuation of insulin or a sulfonylurea at intervals of 0 (baseline), 3, 6, and 12 months. Secondary outcomes included changes in HbA_{1c} and body weight measured at the same intervals of 0 (baseline), 3, 6, and 12 months.

Data were collected using the VA Computerized Patient Record System (CPRS) and stored in a locked spreadsheet. Descriptive statistics were used to analyze the data. Patient data included the number of patients on insulin or a sulfonylurea when initiating a GLP-1 agonist, the percentage of patients started on a certain GLP-1 agonist (dulaglutide, liraglutide, exenatide, and semaglutide), and the percentage of patients with a baseline HbA_{1c} of < 8%, 8% to 10%, and > 10%. The GLP-1 agonist formulary was adjusted during the time of this retrospective chart review. Patients who were not on semaglutide were switched over if they were on another GLP-1 agonist as semaglutide became the preferred GLP-1 agonist.

TABLE Baseline Characteristics (N = 136)

Characteristics	Results
Sex, No. (%)	
Female	4 (3)
Male	132 (97)
Age, mean, y	70.7
Weight, mean, lb	238.2
Hemoglobin A_{1c}	
Mean, %	8.6
< 8%, No. (%)	34 (25.0)
8%-10%, No. (%)	89 (65.4)
> 10%, No. (%)	13 (9.6)
Glucagon-like peptide-1 agonist, No. (%)	
Dulaglutide	27 (19.9)
Liraglutide	12 (8.8)
Exenatide	1 (0.7)
Semaglutide	96 (70.6)

Patients were considered to have a dose reduction or discontinuation of insulin or a sulfonylurea if the dose or medication they were on decreased or was discontinued permanently within 12 months of starting a GLP-1 agonist. For example, if a patient who was administering 10 units of insulin daily was decreased to 8 but later increased back to 10, this was not counted as a dose reduction. If a patient discontinued insulin or a sulfonylurea and then restarted it within 12 months of initiating a GLP-1 agonist, this was not counted as a discontinuation.

RESULTS

This retrospective review included 136 patients; 96 patients taking insulin and 54 taking a sulfonylurea when they started a GLP-1 agonist. Fourteen patients were on both. Criteria for use, which are clinical criteria to determine if a patient is eligible for the use of a given medication, are used within the VA. The inclusion criteria for a patient initiating a GLP-1 agonist is that the patient must have atherosclerotic cardiovascular disease or chronic kidney disease with the patient receiving metformin (unless unable to use metformin) and empagliflozin (unless unable to use empagliflozin).

The baseline mean age and weight for the patient population in this retrospective

FIGURE Patients With a Dose Reduction or Discontinuation of Insulin or Sulfonylurea

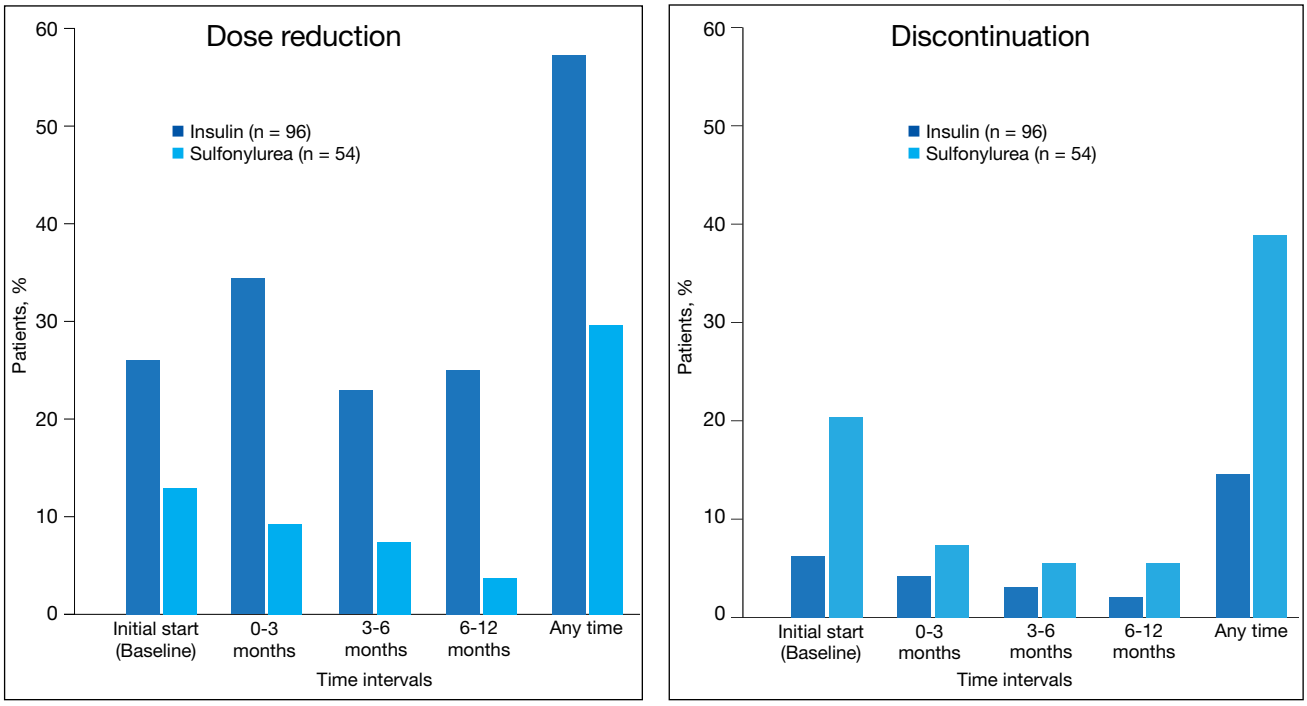

chart review was 70.7 years and 238.2 lb, respectively. Ninety-six patients (70.6%) were started on semaglutide, 27 (19.9%) on dulaglutide, 12 (8.8%) on liraglutide, and 1 (0.7%) on exenatide. The mean HbA_{1c} when patients initiated a GLP-1 agonist was 8.6%. When starting a GLP-1 agonist, 34 patients (25.0%) had an HbA_{1c} < 8%, 89 (65.4%) had an HbA_{1c} between 8% to 10%, and 13 (9.6%) had an HbA_{1c} > 10% (Table).

For the primary results, 25 patients (26.0%) had a dose reduction of insulin when they started a GLP-1 agonist, and 55 patients (57.3%) had at least 1 insulin dose reduction within the year follow-up. Seven patients (13.0%) had a dose reduction of a sulfonylurea when they started a GLP-1 agonist, and 16 patients (29.6%) had at least 1 dose reduction of a sulfonylurea within the year follow-up. Six patients (6.3%) discontinued insulin use when they initially started a GLP-1 agonist, and 14 patients (14.6%) discontinued insulin use within the year follow-up. Eleven patients (20.4%) discontinued sulfonylurea use when they initially started a GLP-1 agonist, and 21 patients (38.9%) discontinued sulfonylurea use within the year follow-up (Figure).

Fourteen patients were on both insulin and a sulfonylurea. Two patients (14.3%) had a dose reduction of insulin when they started a GLP-1 agonist, and 5 (35.7%) had ≥ 1 insulin dose reduction within the year follow-up. Three patients (21.4%) had a dose reduction of a sulfonylurea when they started a GLP-1 agonist, and 6 (42.9%) had ≥ 1 dose reduction of a sulfonylurea within the year follow-up. Seven patients (50.0%) discontinued sulfonylurea and 3 (21.4%) discontinued insulin at any time throughout the year. The majority of the discontinuations were at the initial start of GLP-1 agonist therapy.

The mean HbA_{1c} for patients on GLP-1 agonist was 8.6% at baseline, 8.0% at 0 to 3 months, 7.6% at 3 to 6 months, and 7.5% at 12 months. Patients experienced a mean HbA_{1c} reduction of 1.1%. The mean weight when a GLP-1 agonist was started was 238.2 lb, 236.0 lb at 0 to 3 months, 223.8 lb at 3 to 6 months, and 224.3 lb after 12 months. Study participants lost a mean weight of 13.9 lb while on a GLP-1 agonist.

DISCUSSION

While this study did not examine why there were dose reductions or discontinuations, we can hypothesize that insulin or

sulfonylureas were reduced or discontinued due to a myriad of reasons, such as prophylactic dosing per guidelines, patients having a hypoglycemic event, or pharmacists anticipating potential low blood glucose trends. Also, there could have been numerous reasons GLP-1 agonists were started in patients on insulin or a sulfonylurea, such as HbA_{1c} not being within goal range, cardiovascular benefits (reduce risk of stroke, heart attack, and death), weight loss, and renal protection, such as preventing albuminuria.[13,14]

This retrospective chart review found a large proportion of patients had a dose reduction of insulin (57.3%) or sulfonylurea (29.6%). The percentage of patients with a dose reduction was potentially underestimated as patients were not counted if they discontinued insulin or sulfonylurea. Concomitant use of GLP-1 agonists with insulin or a sulfonylurea may increase the risk of hypoglycemia and reducing the dose of insulin or a sulfonylurea may be necessary.[9-11] The dose reductions in this study show that pharmacists within pharmacy-led PACT clinics monitor for or attempt to prevent hypoglycemia, which aligns with the prescribing information of GLP-1 agonists. While increasing the insulin or sulfonylurea dose is an option for patients, this approach can increase the risk of hypoglycemia, especially in an older population, like this one with a mean age > 70 years. The large proportions of patients with dose reductions or insulin and sulfonylurea discontinuations suggest that pharmacists may need to take a more cautious approach when initiating a GLP-1 agonist to prevent adverse health outcomes related to low blood sugar for older adults, such as falls and fractures.

Insulin was discontinued in 20.4% of patients and sulfonylurea was discontinued in 38.9% of patients within 12 months after starting a GLP-1 agonist. When a patient was on both insulin and a sulfonylurea, the percentage of patients who discontinued insulin (21.4%) or a sulfonylurea (50.0%) was higher compared with patients just on insulin (14.6%) or a sulfonylurea (38.9%) alone. Patients on both insulin and a sulfonylurea may need closer monitoring due to a higher incidence of discontinuations when these diabetes agents are administered in combination.

Within 12 months of patients receiving a GLP-1 agonist, the mean HbA_{1c} reduction was 1.1%, which is comparable to other GLP-1 agonist clinical trials. For semaglutide 0.5 mg and 1.0 mg dosages, the mean HbA_{1c} reduction was 1.4% and 1.6%, respectively.[9] For dulaglutide 0.75 mg and 1.5 mg dosages, the mean HbA_{1c} reduction ranged from 0.7% to 1.6% and 0.8% to 1.6%, respectively.[10] For liraglutide 1.8 mg dosage, the mean HbA_{1c} reduction ranged from 1.0% to 1.5%.[11] The mean weight loss in this study was 13.9 lb. Along with HbA_{1c}, weight loss in this review was comparable to other GLP-1 agonist clinical trials. Patients administering semaglutide lost up to 14 lb, patients taking dulaglutide lost up to 10.1 lb, and patients on liraglutide lost on average 6.2 lb.[9-11] Even with medications such as insulin and sulfonylurea that have the side effects of hypoglycemia and weight gain, adding a GLP-1 agonist showed a reduction in HbA_{1c} and weight loss relatively similar to previous clinical trials.

A study on the effects of adding semaglutide to insulin regimens in March 2023 by Meyer and colleagues displayed similar results to this retrospective chart review. That study concluded that there was blood glucose improvement (HbA_{1c} reduction of 1.3%) in patients after 6 months despite a decrease in the insulin dose. Also, patients lost a mean weight of 11 lb during the 6-month trial.[3] This retrospective chart review at the WBVAMC adds to the body of research that supports potential reductions or discontinuations of insulin and/or sulfonylureas with the addition of a GLP-1 agonist.

Limitations

Several limitations of this study should be considered when evaluating the results. This review was comprised of a mostly older, male population, which results in a low generalizability to organizations other than VA medical centers. In addition, this study only evaluated patients on a GLP-1 agonist followed in a pharmacist-led PACT clinic. This study excluded patients who were prescribed a GLP-1 agonist by an endocrinologist or a pharmacist at one of the community-based outpatient clinics affiliated with WBVAMC, or a pharmacist or clinician outside the VA. The sole focus of this study was patients in a pharmacist-led VAMC clinic. Not all patient

data may have been included in the study. If a patient did not have an appointment at baseline, 3, 6, and 12 months or did not obtain laboratory tests, HbA_{1c} and weights were not recorded. Data were collected during the COVID-19 pandemic and in-person appointments were potentially switched to phone or video appointments. There were many instances during this chart review where a weight was not recorded at each time interval. Also, this study did not consider any other diabetes medications the patient was taking. There were many instances where the patient was taking metformin and/or sodium-glucose cotransporter-2 (SGLT-2) inhibitors. These medications along with diet could have affected the weight results as metformin is weight neutral and SGLT-2 inhibitors promote weight loss.[15] Lastly, this study did not evaluate the amount of insulin reduced, only if there was a dose reduction or discontinuation of insulin and/or a sulfonylurea.

CONCLUSIONS

Dose reductions and a discontinuation of insulin or a sulfonylurea with the addition of a GLP-1 agonist may be needed. Patients on both insulin and a sulfonylurea may need closer monitoring due to the higher incidences of discontinuations compared with patients on just 1 of these agents. Dose reductions or discontinuations of these diabetic agents can promote positive patient outcomes, such as preventing hypoglycemia, minimizing weight gain, increasing weight loss, and reducing HbA_{1c} levels.

Acknowledgments

This material is the result of work supported with resources and the use of facilities at the Wilkes-Barre Veterans Affairs Medical Center in Pennsylvania.

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The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

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Ethics and consent

It was determined that this project description approval by an institutional review board or other review committee was not needed. The project was a nonresearch Veteran Health Administration operations activity.

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