A Retrospective Review of Concomitant Use of Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors

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Estimates of the global burden of diabetes exceed 530 million adults with type 2 diabetes mellitus (T2DM), accounting for more than 95% of total cases worldwide.[1,2] In Lancaster General Health Physicians (LGHP) practices, there are approximately 32,000 patients living with diabetes. Over the past two decades, novel agents for management of T2DM have come to market, and the guidelines for management of individuals with diabetes have changed significantly as a result.[3,4] Two novel classes of medications acting on the incretin pathway are dipeptidyl-peptidase-IV (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

DPP-4 inhibitors are oral agents that improve glycemic control via inhibition of the DPP-4 enzyme, which decreases the breakdown of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).[5] GLP-1 RAs, given orally or subcutaneously, directly activate the GLP-1 receptor to stimulate insulin secretion from the pancreatic beta cells.[5,6] Due to the overlapping pathway within the incretin system, concomitant use of DPP-4 inhibitors and GLP-1 RAs is considered a duplication of therapy.[3] When comparing simultaneous use of these agents versus monotherapy of either class alone, patients experience modest improvements in glycemic control and minimal additional weight loss.[7,8]

In one study, sitagliptin was added to liraglutide therapy, and although GLP-1 and GIP concentrations increased, marginal, non-significant changes were seen in glycemic levels.[5] Another published case series of patients with T2DM taking once-weekly GLP-1 RAs and simultaneous DPP-4 inhibitors demonstrated a median change in glycosylated hemoglobin A1c (HgbA1c) of –0.8% (interquartile range [IQR] = –4.3% to 2%). In the analysis, 28% of patients experienced gastrointestinal adverse reactions and 17% experienced hypoglycemia symptoms.[7]

As these two drug classes are more expensive compared to alternative non-insulin medications used to treat diabetes, the concomitant use of GLP-1 RAs and DPP-4 inhibitors can lead to excessive medication costs for both patients and the health care system.[5] For example, using the local zip code and price estimates from GoodRx, a four-week supply of brand dulaglutide costs $1,039 and 30 tablets of brand sitagliptin 100 mg cost $342, while a 30-day supply of extended-release metformin (at 2,000 mg/day) costs $8 and 30 tablets of glipizide ER 5 mg cost $9. Therefore, it is reasonable to review instances in which GLP-1 RAs and DPP-4 inhibitors are being used together with the intent of reducing the concomitant use of these drug classes.

Penn Medicine Lancaster General Health is a rural community health system located in Pennsylvania that serves Lancaster County as well as several surrounding counties. There are 15 ambulatory clinical pharmacists embedded within 12 of 28 LGHP Family Medicine practices; these pharmacists practice under collaborative drug therapy management (CDTM) agreements.

In the electronic health record (EHR), a duplicate therapy warning is triggered at the time of prescribing to discourage the concomitant use of GLP-1 RAs with

DPP-4 inhibitors. Prescribers must acknowledge the interaction to bypass the alert in order to prescribe two agents from these drug classes at the same time. They are able to enter additional clarifying information regarding why they are prescribing both classes together; this warning is therefore not a hard stop (see Fig. 1).

METHODS

This single-center retrospective review was conducted across LGHP Family Medicine practices and was approved by the Lancaster General Hospital Institutional Review Board. An Epic SlicerDicer report was utilized to identify adult patients who had both a DPP-4 inhibitor and a GLP-1 RA or GLP-1/GIP dual agonist on their active medication list from January 1, 2023, to July 31, 2023.

Of the patients identified, the EHR dispense report was reviewed to determine if patients were actively filling both medications based on claim information from the dispensing pharmacy. Prescriber notes were reviewed to ensure appropriate inclusion of patients concomitantly prescribed and filling both agents.

Patients were included if they were over the age of 18 years and if the active prescriptions for the DPP-4 inhibitor and GLP-1 RA were both being filled simultaneously for at least one month. Combination products, such as those with a DPP-4 inhibitor plus metformin, were also included. Patients were excluded if they were seen by a primary care clinician outside of LGHP or if they were deceased.

Key data points collected include patient demographics and insurance type, primary care clinician and office location, whether the patient was seen by an ambulatory clinical pharmacist in the past year, the active medication list, time between initiation of first and second agent, outpatient pharmacy information, and pertinent glycosylated HgbA1c values.

Three HgbA1c values were reviewed. The first (HgbA1c #1) was obtained prior to initiation of the first agent; the second (HgbA1c #2) was obtained while on the first agent but prior to initiation of the second agent; the last (HgbA1c #3) was the most recent HgbA1c value obtained after initiation of the second agent. The minimum time between each HgbA1c was three months.

The primary outcome of this study was to determine the frequency of patients who were prescribed and filling both DPP-4 inhibitors and GLP-1 RAs. Secondary outcomes included the rate of occurrence at an outpatient practice with versus without an integrated CDTM ambulatory clinical pharmacist, impact of use pattern on HgbA1c, and adverse events potentially due to concomitant use of DPP-4 inhibitors and GLP-1 RAs. All outcomes were compared utilizing descriptive statistics (average, standard deviation).

At the conclusion of the study, ambulatory clinical pharmacists contacted the prescribers of these 28 individuals via the electronic health record and recommended discontinuation of the DPP-4 inhibitor.

RESULTS

From the initial report, 138 patients were identified to have both a DPP-4 inhibitor and GLP-1 RA on their active medication list in the specified timeframe. Baseline patient demographics and characteristics are listed

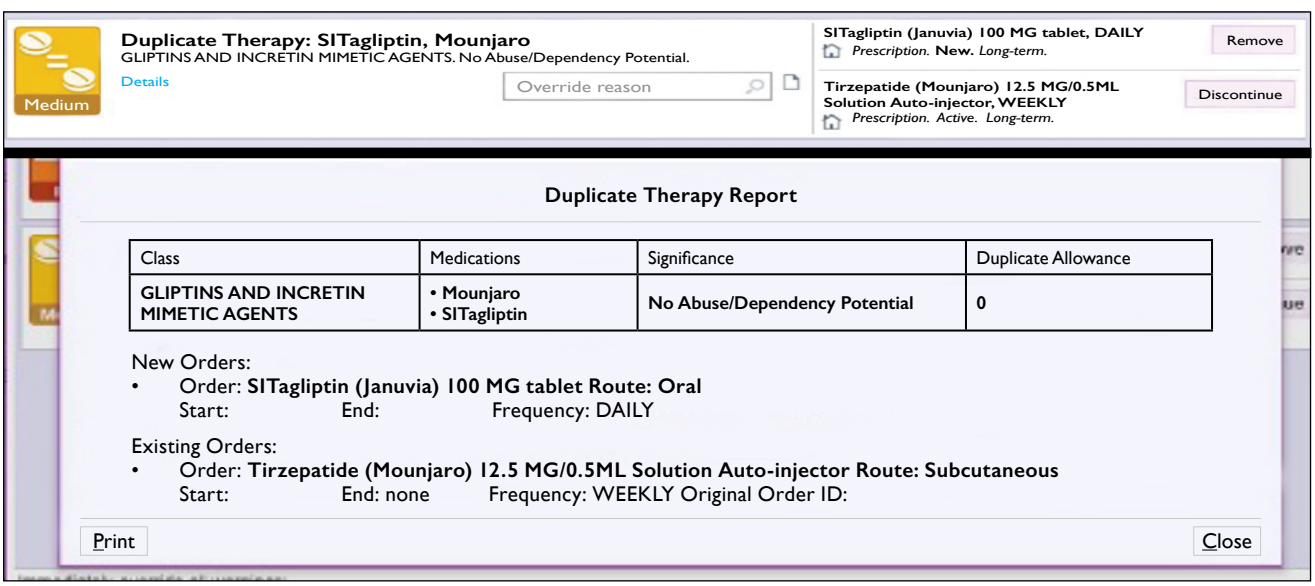

Fig. 1. Epic warning that fires when GLP-1 RAs and DPP-4 inhibitors are simultaneous active prescriptions.

in Table 1. Of the 138 patients identified to have both a DPP-4 inhibitor and GLP-1 RA on their active medication list, 28 (20%) were found to be actively filling both agents. The DPP-4 inhibitors, GLP-1 RAs, and combination products that were revealed to be co-prescribed during the review are detailed in Table 2 on page 50.

Sixteen (57%) of the 28 patients actively filling medications from both drug classes received care at a site without a CDTM ambulatory clinical pharmacist embedded within the practice. None of the patients were seen by an ambulatory clinical pharmacist or an endocrinologist within one year from the start of the enrollment period.

The majority of patients who had both drug classes on their active medication list were not actively filling both medications concomitantly but rather were transitioned from one drug class to the other. Notably, there was one patient identified to be actively filling and taking two DPP-4 inhibitors and one GLP-1 RA.

As seen in Fig. 2 on page 51, the median HgbA1c #1, HbgA1c #2, and HgbA1c #3 was 9.00% (IQR = 7.60-9.95), 9.10% (IQR = 7.98-9.53), and 7.65% (IQR = 6.85-9.05), respectively. The first agent prescribed in 25 out of 28 patient cases was a DPP-4 inhibitor. After the first agent was added, the median HgbA1c increased by 0.10%. After the initiation of the second agent, the median HgbA1c decreased by 1.45% to 7.65%.

The start of the first agent was recorded by either the first time the prescription was ordered or, if they were started on it outside of LGHP, the first time it was noted in the patient's chart. There was a median of 25.5 months (IQR = 34.7) from the time the first agent was started to the addition of the second agent, and there was a wide range of 3 months to 93 months. The duration of overlap of both agents was collected, and there was a median of 20 months (IQR = 52.3) of patients taking a DPP-4 inhibitor and a GLP-1 RA concomitantly.

Adverse events possibly attributable to the concomitant therapy of both a DPP-4 inhibitor and a GLP-1 RA were discovered in one patient, who reported experiencing diarrhea during a follow-up visit per clinician documentation. There was no additional documentation by the primary care clinician regarding symptom onset, and no changes were made to the patient's medication regimen. Based on this limited information, it is not possible to say if the patient's diarrhea was due to either agent alone or the combination.

Table 1. Baseline Demographics of Individuals Actively Filling Both Medication Types During Study Period

Baseline Characteristics of Patients	n = 28
Gender - # (%)	
Female	14 (50)
Male	14 (50)
Age (Median)	62.9 years
Body Mass Index (Average)	34.3 kg/m^2
Diagnosis of Type 2 Diabetes Mellitus - # (%)	28 (100)
Current Diabetes Mellitus Medications - # (%)	
DPP-4 inhibitor	28 (100)
GLP-1 RA	26 (93)
GLP-1 RA/GIP	2 (7)
Insulin, basal	6 (21)
Insulin, bolus	0
Metformin	16 (57)
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors	9 (32)
Sulfonylureas	9 (32)
Thiazolidinediones	0
Meglitinides	0
Insurance Type - no. (%)	
Commercial	11 (39)
Medicare	14 (50)
Dual Medicare/Medicaid	3 (11)

LIMITATIONS

This study had several limitations, including the retrospective nature of chart reviews within the EHR and the smaller sample size of patients included in the secondary evaluation. Reports of adverse effects were low, which could be due to a lack of documentation. In addition, regarding patients who were not started on therapy within this health system, the first HgbA1c value and the duration of therapy could only be collected based on first documentation of the agents in the chart. There was only one individual who did not have an accessible HgbA1c in the EHR prior to initiating the first medication.

Many patients in this review had been on both agents for several years. The decrease in some patients' HgbA1c values could be due to lifestyle modifications or the initiation of other additional agents, including insulin, during this time, but this cannot be known for

certain. It was also not known if the doses used for GLP-1 RAs were titrated appropriately. Knowing the doses of the medicines relative to the HgbA1c could have helped determine if the doses were titrated to target.

It is not known how many patients in these practices who had diabetes were strictly on treatment with one of these agents exclusive of the other class.

Despite these limitations, the data presented show a role for ambulatory clinical pharmacist intervention to improve the prescribing of these medication classes.

DISCUSSION

Despite 138 patients being identified with a DPP-4 inhibitor plus a GLP-1 RA on their medication list, only 20% of them were filling both medications. This demonstrates the need for improved medication reconciliation practices to increase medication list accuracy. Pharmacists can play a vital role in the medication reconciliation process. It is possible that some prescribers may leave both drug classes on the medication list to allow for prior authorizations or for the patient to determine if the new medication is cost feasible. However, in many patients there was no follow-up to remove one of the medications from the list.

The first agent prescribed in 25 out of 28 patients (89.3%) was a DPP-4 inhibitor. This could be due to the timeline of market approvals in the United States (the first DPP-4 inhibitor was approved in 2006, versus 2009 for the first GLP-1 RA) and that DPP-4 inhibitors are oral agents while most GLP-1 RAs are injectable. The first oral GLP-1 RA (oral semaglutide) did not become available until 2019.

The average HgbA1c #1 (prior to initiation of the first DPP-4 inhibitor or GLP-1 RA) was 8.84% (SD ±1.73%). After the first agent was added, the average HgbA1c increased by 0.1%. This change is minimal given that most patients started with an HgbA1C >8% and most patients have an Hgb-A1C goal of either <7% or <8%.[3]

With the initiation of the second agent, which was typically the GLP-1 RA in this review, the average HgbA1c decreased to 7.86% (SD ±1.35%). While this is a reduction, it is not quite what would be expected by solely adding a GLP-1 RA to a patient's regimen. Since the doses of prescribed medicines were not noted during the course of this study, it is possible that the reduction in HgbA1c would have been of greater magnitude if GLP-1 RAs had been titrated to the maximally tolerated doses.

Table 2. DPP-4 Inhibitor and GLP-1 RA Agents of Interest

DPP-4 Inhibitor Agents	GLP-1 RA Agents
Sitagliptin	Dulaglutide
Saxagliptin	Liraglutide
Linagliptin	Semaglutide
Alogliptin	Exenatide
	Lixisenatide
	Tirzepatide (dual GLP-1/GIP RA)
Combination Products	
Alogliptin and metformin	
Alogliptin and pioglitazone	
Dapagliflozin and saxagliptin	
Empagliflozin and linagliptin	
Empagliflozin, linagliptin, and metformin	
Empagliflozin and sitagliptin	
Linagliptin and metformin	
Saxagliptin and metformin	
Sitagliptin and metformin	
Insulin degludec and liraglutide	
Insulin glargine and lixisenatide	

Historically, GLP-1 RAs lower HgbA1C by >1%, and some studies have shown HgbA1C-lowering potential as much as 2%.[3,9-11] This raises questions as to whether therapies were uptitrated according to the approved product labeling and if patients were adherent to their medications. Nonetheless, our results are consistent with the known greater glycemic-lowering potential of GLP-1 RAs compared to DPP-4 inhibitors.

After the identification of patients actively filling both medications, ambulatory clinical pharmacists contacted the prescribers to recommend discontinuation of the DPP-4 inhibitors.

While the cost of DPP-4 inhibitors and GLP-1 RAs is historically similar, clinicians should consider the preferential health outcomes that are associated with GLP-1 RAs. Several GLP-1 RAs have demonstrated cardioprotective effects including reductions in major cardiovascular (CV) events such as non-fatal myocardial infarction, non-fatal stroke, and CV death.[3,9,11-15]

Outcome trials of DPP-4 inhibitors have not demonstrated that these medicines lead to CV benefits, and while a potential increase in heart failure hospitalizations among individuals prescribed DPP-4 inhibitors has been shown, the data have not been consis-

tent; current guidelines recommend DPP-4 inhibitors not be used in patients with heart failure.[16-19] GLP-1 RAs promote more weight loss compared to DPP-4 inhibitors; this may be another reason to prefer this drug class, given the prevalence of obesity in patients with T2DM.[3,9] Deprescribing either medication will also reduce medication use burden and medication costs to the patient.

Based on the results of this medication use evaluation, ambulatory clinical pharmacists made 28 recommendations to primary care clinicians regarding duplication of therapy which resulted in an acceptance rate of 78.5%. One of the 28 recommendations was acknowledged without any change made; the remaining five were declined. In the cases of declination, clinicians cited no adverse effects and patient preference as justification to continue. In all cases that were accepted, the DPP-4 inhibitor was the medication that was subsequently discontinued.

One case of interest involved a patient who was prescribed two DPP-4 inhibitors in addition to one GLP-1 RA. In this case, there were no notes in the patient's chart from the clinician elucidating why the patient would be on this regimen.

The majority of the clinicians treating patients with both a DPP-4 inhibitor and a GLP-1 RA do not have an embedded clinical pharmacist in their practice. In our health system, clinical pharmacist involvement with diabetes management is dependent upon clinician referrals, and approximately half of the Family Medicine practices do not have a dedicated ambulatory clinical pharmacist. Due to the limited number of ambulatory clinical pharmacist full-time equivalents and competing priorities, many clinicians do not have access to or interact with pharmacist clinicians on a regular basis.

As described in this report, there is a role for ambulatory clinical pharmacists to promote evidence-based prescribing. It is well established that embedding pharmacists in primary care practices results in improved patient outcomes as well as decreased health care costs. One study identified a 1.75% decrease in HgbA1c for patients treated in a physician-pharmacist collaborative care group compared to an average 0.16% decrease in HgbA1C among patients treated in a usual care group without a pharmacist involved ($p < 0.05$).[20]

The ambulatory clinical pharmacists at LG Health who are embedded in Family Medicine practices manage diabetes for patients under a CDTM agreement. It is notable that no patients found to be taking drugs from both medication classes were seen by an ambulatory clinical pharmacist during the study period. With additional pharmacist resources, pharmacists would be able to provide medication management services to all Family Medicine practices and potentially reduce inappropriate prescribing.

Using available payor data, we calculated potential cost savings from recommended interventions for both LG Health and patients. The estimated cost to LG Health for the use of an unnecessary DPP-4 inhibitor over the course of a year is more than $5,000. From the data presented, if all interventions were accepted by the clinicians, then the health care system savings could exceed $180,000 per year. Some recommendations were accepted, and those pharmacist-initiated interventions resulted in an estimated cost savings of approximately $115,000 to the health care system per year and approximately $600 to each patient per year. Patient savings is valued based on an estimated monthly copay.

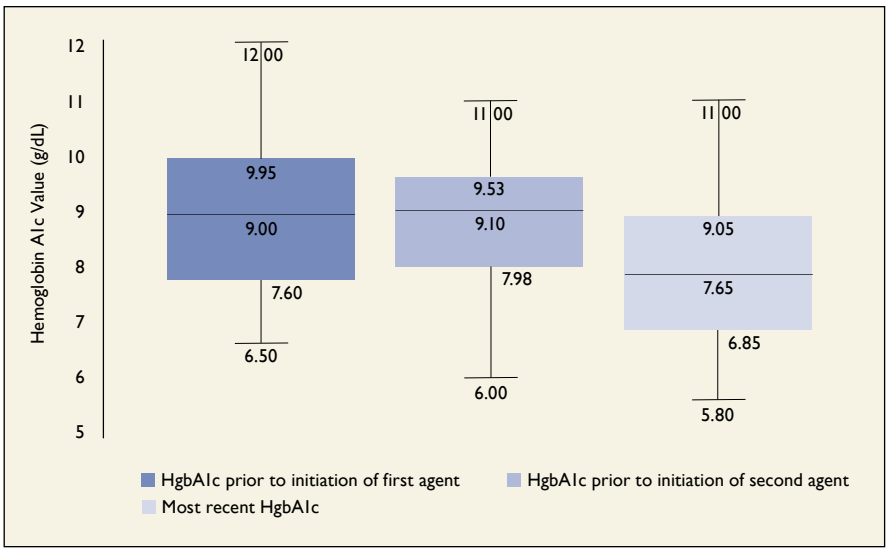

Fig. 2. Average glycosylated hemoglobin A1c (HgbA1c) at specified time points of individuals who were actively filling both medication types during the study.

CONCLUSION

The results of this retrospective chart review demonstrate that despite guidelines and literature advising against concomitant use of GLP-1 RA and DPP-4 inhibitors, they are still prescribed together.

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