



Chronic Medication Burden and Complexity for US Patients with Type 2 Diabetes Treated with Glucose-Lowering Agents

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ABSTRACT

Introduction: Most adults with type 2 diabetes (T2D) have several chronic conditions treated with complex regimens and multiple medications. The burden and complexity of multiple medication use are associated with worse patient outcomes, including reduced adherence and increased costs, hospitalizations, mortality rates, and HbA1c. This study quantifies the chronic medication burden, regimen complexity, and potential medication interactions in patients with T2D using a nationwide claims database in the USA.

Methods: Adults with T2D treated for greater than half of the year with at least one glucose-lowering agent (GLA) in 2017 were included in this descriptive study. Chronic medications were defined as all GLAs and non-GLA

medications prescribed for at least 90 days in 2017 to at least 2% of the cohort. Medication burden, defined as the number of medications prescribed, was examined. Medication complexity, proxied by the Medication Regimen Complexity Index (MRCI), and potential use of interacting medications were also examined. Results were investigated for all chronic medications and were reported on the basis of the disease treated (diabetes or other condition) and the route of administration (oral or other).

Results: On average, in 2017, the 814,156 patients included in the study filled prescriptions for 4.1 chronic medications (standard deviation [SD] = 2.0), 3.7 oral chronic medications (SD = 1.9), 1.5 GLAs (SD = 0.8), and 1.1 oral GLAs (SD = 0.7). The average MRCI was 14.7 for all chronic medications (SD = 7.4), with a mean of 12.4 for all oral chronic medications (SD = 6.3), 6.6 for all GLAs (SD = 3.8), and 4.9 for oral GLAs (SD = 2.6).

Conclusion: On average, patients with T2D used multiple medications, had a complex medication regimen, and were at potential risk of medication interactions. These findings suggest that patients, practitioners, pharmacists, and payers may benefit from interventions which decrease medication burden, complexity, and/or adverse events related to the treatment of T2D.

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Medication interactions; Medication regimen complexity index; Polypharmacy; Type 2 diabetes

Key Summary Points

Why carry out this study?

Most patients with type 2 diabetes (T2D) have several chronic conditions treated with complex regimens and multiple medications.

The medication burden and medication complexity associated with the use of multiple medications are associated with worse patient outcomes, including reduced adherence, increased mortality, higher HbA1c, and an increased likelihood of medication interaction adverse events.

This study quantifies chronic medication burden, regimen complexity, and medication interactions in patients with T2D using a nationwide claims database in the USA.

What was learned from the study?

Patients with T2D used multiple medications, had a complex medication regimen, and were at noteworthy potential risk of medication interactions.

Given that medication burden and complexity are associated with poorer adherence and worse patient outcomes, the findings suggest that patients, practitioners, pharmacists, and payers may benefit from interventions capable of decreasing medication burden, complexity, and/or adverse events related to the treatment of T2D.

INTRODUCTION

Type 2 diabetes (T2D) is a complex and progressive disease [1] that currently affects nearly 30 million Americans [2]. Given its progressive nature, treatment algorithms recommend sequential medication additions to maintain glycemic control [3]. T2D commonly co-occurs with a number of other chronic conditions, such as hypertension, hyperlipidemia, and cardiovascular disease [4]. Among patients with T2D, concurrent treatment of chronic comorbidities elevates the medication burden [5].

Use of more medications and increased complexity of medication regimens have been found to be associated with worse outcomes, including reduced patient adherence [6, 7]. Specifically, a comprehensive review of 76 studies found that mean adherence decreased progressively from 79% with once-daily dosing to 51% with four times per day dosing [6]. Other research specific to patients with T2D found that lower scores of treatment complexity were associated with adherence to glucose-lowering agents (GLAs), while higher scores were associated with non-adherence ($P = 0.04$) [7]. Increased medication burden or complexity has also been found to be associated with increased HbA1c and healthcare costs, as well as with higher mortality rates among elderly individuals [8–11]. For example, a meta-analysis of 16 studies of elderly patients with T2D found that polypharmacy was associated with a significant increase in the likelihood of all-cause mortality [odds ratio (OR) = 1.62; 95% confidence interval (CI) 1.61–1.64 [8], while a more general study of older adults found that increased medication complexity was associated with all-cause mortality (adjusted hazard rate = 1.12; 95% CI 1.01–1.25) [10]. Additional research has reported an association between reduced medication regimen complexity and significant improvement of HbA1c at 3 months' follow-up, with mean HbA1c lowered from 7.7% [standard deviation (SD) = 0.4%] before to 6.9% (SD = 0.4%) after the regimen simplification ($P < 0.0001$) [11]. A longer-duration study of patients aged 65 years or older with diabetes found that those treated with more than 10

medications had a 0.04% reduction in HbA1c over 2 years and a 15.0% mortality rate compared to a 3.01% reduction in HbA1c and a 13.3% mortality rate for patients treated with five or fewer medications [12]. Furthermore, a cross-sectional study of patients aged 60 or older showed that individuals prescribed six or more medications were significantly more likely to have a medication interaction (OR 10.37; 95% CI 3.35–32.11) [13]. Similarly, the number of medications dispensed was the factor most strongly associated with the greater than 125% increase in the rate of potentially serious medication interactions that occurred in Scotland from 1995 to 2010 (from 5.8% to 13.1%) [14].

Much of the previous research examining medication burden and complexity in patients with T2D has focused on relatively small patient populations and has measured medication use at a single point in time or using patient recall. This research used a large administrative claims database to longitudinally capture the medication burden, complexity, and potential medication interactions of patients with T2D. The study was based upon the actual filled prescriptions for chronic medications and included patients across the USA.

METHODS

This retrospective, descriptive study first identified the cohort of interest using the IBM[®] MarketScan[®] Commercial Claims and Encounters and Medicare Supplemental databases. These administrative claims databases collect information from employers and health plans, and include data on patient characteristics, inpatient and outpatient diagnoses, procedures, and outpatient prescription medication use [15]. All the data is fully de-identified and compliant with the Health Insurance Portability and Accountability Act (HIPAA). This data was made available by license agreement between IBM[®] and Eli Lilly and Company.

The study focused on the calendar year 2017 and included patients with T2D who were treated with a GLA for at least half of the year. Patients were identified as having T2D if they received two or more diagnoses of T2D (ICD-9-

CM of 250.x0 or 250.x2 or ICD-10-CM of E11xx) or one diagnosis of T2D along with no more than one diagnosis of type 1 diabetes (T1D) (ICD-9-CM 250.x1 or 250.x3 or ICD-10-CM of E10xx) and filled at least one prescription for an oral GLA [16]. Patients were excluded if they were diagnosed as pregnant at any time in 2017, younger than 18 as of January 1, 2017, or uninsured at any time in 2017. These inclusion and exclusion criteria resulted in a sample of 814,156 patients. Supplementary Fig. S1 illustrates how the inclusion and exclusion criteria affected sample size.

The IBM[®] MarketScan[®] databases were also used to identify medications of interest. To be identified as a treatment for a chronic condition and included in the study, a medication had to be either a GLA used for the treatment of diabetes or a medication where prescriptions were filled by least 2% of the cohort for at least 90 days in 2017. Given these criteria, the study included 107 different chronic medications used to treat diabetes or other chronic conditions (Table 1). All 107 chronic medications were categorized as a treatment for diabetes (GLAs) or another chronic condition (non-GLAs), and the medications were furthermore grouped according to their route of administration (oral or other). Supplementary Table S1 provides the complete list of medications identified as chronic medications for our analyses.

Given the patient population and list of chronic medications, the analyses examined for patient characteristics, including demographics, general health, and comorbidities. Demographics of interest included age, sex, region of residence, and insurance plan type. General health was proxied by the Charlson Comorbidity Index (CCI) while the severity of diabetes was assessed using the Diabetes Complications Severity Index (DCSI). The CCI creates a composite morbidity score that reflects mortality risk [17] based upon the presence of any of 19 comorbidities, each scored on a scale of 1–6 [18]. The DCSI is a 13-point scale calculated from patient medical records and designed to quantify the severity of diabetes-related complications and to predict the risk of adverse outcomes in people with diabetes [19, 20]. In addition to examining general health using the

Table 1 Patient characteristics

Characteristic	Mean \pm SD or N (%)
Sample size	814,156
Age	59.7 \pm 11.7
Sex	
Female	371,007 (45.6)
Male	443,149 (54.4)
Region	
Northeast	140,440 (17.3)
North Central	193,310 (23.7)
South	388,256 (47.7)
West	90,097 (11.1)
Unknown	2053 (0.3)
Insurance type	
Comprehensive	115,769 (14.2)
Exclusive provider organization	5977 (0.7)
Health maintenance organization	88,500 (10.9)
Point of service	64,427 (7.9)
Preferred provider organization	410,876 (50.5)
Point of service with capitation	11,068 (1.4)
Consumer directed health plan	74,308 (9.1)
High deductible health plan	40,072 (4.9)
Unknown	14,227 (1.8)
Charlson Comorbidity Index	2.7 \pm 2.1
Diabetes Complications Severity Index	1.4 \pm 2.0
Comorbidities	
Anxiety	87,535 (10.8)
Arthritis—rheumatoid or psoriatic	16,460 (2.0)
Asthma	56,859 (7.0)
Benign prostatic hyperplasia	57,308 (7.0)
Chronic obstructive pulmonary disease	50,454 (6.2)
Depression	89,141 (10.9)

Table 1 continued

Characteristic	Mean \pm SD or N (%)
Epilepsy/seizures	9258 (1.1)
Gastroesophageal reflux disease	126,644 (15.6)
Glaucoma	86,728 (10.7)
Gout	28,903 (3.6)
Heart failure	47,388 (5.8)
High cholesterol	620,854 (76.3)
Hypertension	640,127 (78.6)
Hypoglycemia	10,361 (1.3)
Hypokalemia	19,386 (2.4)
Hypothyroidism	134,755 (16.6)
Insomnia	28,995 (3.6)
Pain—chronic or acute	51,292 (6.3)
Rhinitis—seasonal or non-seasonal	76,423 (9.4)
Thrombosis	3534 (0.4)

SD standard deviation

CCI and DCSI, the analyses examined specific comorbidities present in this population based upon the chronic medications used for the cohort. These comorbidities included hypertension, hyperlipidemia, anxiety, depression, gastroesophageal reflux disease, glaucoma, and hypothyroidism, among others (see Table 1 for a complete list).

In the main analyses, this study defined medication burden on the basis of two calculations: (1) the mean number of chronic medications prescribed per patient, per day, and (2) the mean number of days that a given quantity of chronic medications was prescribed. To calculate the mean number of medications take per patient, per day, the analyses determined the total number of medications each patient was prescribed and filled a prescription for, and the average burden was calculated as the sum of the number of medications prescribed and dispensed each day in the calendar year 2017 and then divided that sum by 365. Given our focus

on patient burden, fixed-dose combination medications, which contain multiple active ingredients in a single dosage form, were counted as one medication. For all therapies, medication use was identified in the claims database by the prescription fill date, quantity supplied, and days' supply fields. If a patient filled a second prescription prior to the expected end date of the first prescription, it was assumed that the second prescription was filled early and would not be taken until the expected end of the first prescription.

Medication burden was also examined on the basis of the average number of days patients were treated with a specific number of medications. Specifically, the analyses examined how many days in 2017 a patient was treated with no chronic medication, one chronic medication, two chronic medications, and so on, through eight or more chronic medications. As with the average medication burden per patient, these observations were classified according to indication (diabetes or other) and route of administration (oral or other).

The analysis furthermore determined the average medication complexity using the Medication Regimen Complexity Index (MRCI). The MRCI is a validated instrument that focuses on factors known to influence patient adherence [21]. Following MRCI protocol, three components of complexity were assessed: (1) dosage form, (2) frequency of dosing, and (3) administration instructions.

The first component of the MRCI, dosage form, was calculated by assigning each medication a score from 1 to 5 depending upon dosage form. Capsules and tablets, for example, received a score of 1. Nebulizers, representing a more complex dosage form, received a score of 5. The second component of the MRCI, dosing frequency, was scored on a scale from 0.5 to 12.5 based on the prescribed frequency of administration. For instance, medications prescribed to be taken once daily received a score of 1, whereas medications to be taken four times per day received a score of 4. The third component of the MRCI, additional directions, was scored on a scale from 0 to 12, with each component that was present given a score of 1 or 2. If a medication needed to be altered in any way

(e.g., broken, crushed, dissolved), if multiple units need to be taken at once, if the medication must be taken at a specific time or in relation to food or liquid, or if there was variable dosing, the additional components score was increased by 1. The additional directions component would increase by 2 if the medication dosage was tapered or increased, if there was alternate dosing, or if the prescription included instructions to "take/use as directed." Supplementary Table S5 provides the complete scoring for the MRCI.

When calculating the MRCI, information from the claims databases was supplemented using data from Facts and Comparisons [22]. As a retrospective study which used de-identified data, the study did not seek institution review board approval. Permission to access data from IBM and Walters Kluwer was obtained via purchase of data licenses.

This data was available by license agreement between HealthMetrics Outcomes Research and Walters Kluwer. All components of the MRCI were obtained from Facts and Comparisons except the dosing frequency and information on tapering/increasing medications, which were obtained from the actual filled prescription records. Each medication was independently scored by a health outcomes analyst and a nurse, and any differences were then reconciled. As an additional data quality check, each score was then independently reviewed by a licensed pharmacist.

Finally, the study also examined medication interactions. A potential medication interaction was identified as any two chronic medications for which, according to Facts and Comparisons: (a) therapy should be monitored, (b) therapy modification should be considered, or (c) the combination of the two medications should be avoided. When Facts and Comparisons listed classes of therapies instead of individual medications, DrugBank [23], a free online resource, was used to identify each of the individual medications in the class of interest. For each of the chronic medications included in the analyses, the number of potential medication interactions was calculated, and the average number of medication interactions was calculated as the sum of all potential interacting medications

divided by the number of chronic medications examined.

Given the study objectives, the analyses were purely descriptive in nature. For all variables, means and standard deviations were provided, as were medians and interquartile ranges. Differences in medication burden and MRCI were examined using *t* tests when comparing differences across age groups and analysis of variance tests (ANOVAs) when comparing differences across region or insurance type (Supplementary Tables S2–S4). A *p* value less than 0.05 was considered, a priori, to be statistically significant. As a retrospective investigation that used de-identified data, the study did not seek institution review board approval. All analyses were conducted using SAS, v. 9.4 (Cary, NC).

RESULTS

Table 1 presents the characteristics of patients included in the study. The mean age was 59.7 years (SD = 11.7 years), and more patients were male (54.4%). Patients most commonly resided in the Southern region of the USA (47.7%) and were most commonly insured via a preferred provider organization (50.5%). Based upon diagnoses in 2017, the average CCI was 2.7 (SD = 2.1), and the average DCSI was 1.4 (SD = 2.0). Patients were most frequently diagnosed with comorbid hypertension (78.6%), hyperlipidemia (76.3%), hypothyroidism (16.6%), gastroesophageal reflux disease (15.6%), depression (10.9%), anxiety (10.8%), and glaucoma (10.7%).

Figures 1 and 2 illustrate the burden of all chronic medications and GLAs. The overall mean medication burden per patient was 4.1 medications per day (Fig. 1), and most of the burden was related to use of chronic conditions other than T2D, such that only 1.5 out of the average of 4.1 medications were GLAs. The majority of the medication taken orally, with the mean total oral medication burden equal to 3.7 and the average oral GLA medication burden equal to 1.1. Figure 2 illustrates the average percentage of days patients were prescribed from zero to eight chronic medications. As Fig. 2 shows, in 2017, patients most frequently

filled prescriptions for four chronic medications (17.6% of days), three oral chronic medications (19.0% of days), and one oral GLA (51.9% of days) or GLA of any kind (48.2% of days).

While Figs. 1 and 2 illustrate medication burden, Fig. 3 and Table 2 examine the complexity of the medication regimens for patients with T2D. Figure 3 illustrates the average total MRCI score both for GLAs and for all chronic medications, breaking out oral use and all-medication use. Table 2 shows each of the individual components of the MRCI. The average MRCI score was 14.7 for all prescriptions filled for chronic medications, with a mean of 12.4 for oral chronic medications, 6.6 for GLAs, and 4.9 for oral GLAs. As Table 2 illustrates, for all medication groups examined, dosing frequency comprised the largest component of the MRCI.

Differences in medication burden and the MRCI were also examined for patients on the basis of age, region of residence, and type of insurance coverage. These results illustrate that, in general, medication burden, MRCI total score, and MRCI component score are significantly higher for patients aged 65 years or older compared to patients who are younger than age 65. In addition, medication burden and MRCI were found to be higher for patients residing in the North Central region of the USA as well as patients with comprehensive insurance. In contrast, the patients with lower medication burden and complexity generally resided in the Western region of the USA or whose region of residence was unknown and more frequently had high deductible health plans. Supplementary Tables S2–S4 provide the complete results.

In addition to examining medication burden and regimen complexity, this study also looked at the potential for medication interactions. On average, there were 24.9 potential medication interactions among the 107 chronic medications examined. In percentage terms, these findings suggest that nearly one-quarter (23.3%) of the 107 medications examined had the potential to interact with another of the medications included in the study.

Finally, as a test of the robustness of the results, the primary analyses were repeated with a more inclusive definition of chronic

medications. Specifically, in the second set of analyses, chronic medications included all GLAs and all medications prescribed to at least 2% of the population for 30 days or more in 2017. This less restrictive criterion resulted in the addition of 15 medications. However, the main results did not change substantially. For example, average medication burden increased from 4.1 (SD = 2.0) to 4.3 (SD = 2.1), and average total MRCI increased from 14.7 (SD = 7.4) to 15.2 (SD = 7.7). In addition, a second sensitivity analysis removed the assumption that if a patient filled a second prescription prior to the expected end of the first prescription, the second prescription was not started until the expected end of the first prescription. Instead, this sensitivity analysis assumed that the patient started the second prescription on the date that the prescription was filled. This change in assumption resulted in a slight reduction in estimates of medication burden and MRCI. For example, the average medication burden decreased from 4.1 (SD = 2.0) to 4.0 (SD = 1.9) and the average total MRCI decreased from 14.7 (SD = 7.4) to 14.2 (SD = 7.2).

DISCUSSION

This study explored the burden, complexity, and potential for interactions associated with chronic medication therapy for patients with T2D. The results revealed that pharmaceutical treatment for T2D is associated with polypharmacy, a high degree of complexity, and a significant potential for interactions.

In this population, the medication burden was large, with the average number of chronic prescription medications taken per day equal to 4.1, and patients taking, on average, six or more medications per day for over 25% of the year. This evidence is consistent with previous research showing a high medication burden among German patients with T2D [24]. Notably, antidiabetic medications represented slightly less than one-half of the overall chronic medication burden in the present study, in concert with previous evidence indicating that many patients with T2D are also diagnosed with chronic comorbidities [4, 25] and that GLA use represents less than half of the medication burden for patients with T2D [9]. In previous studies, greater medication burden among

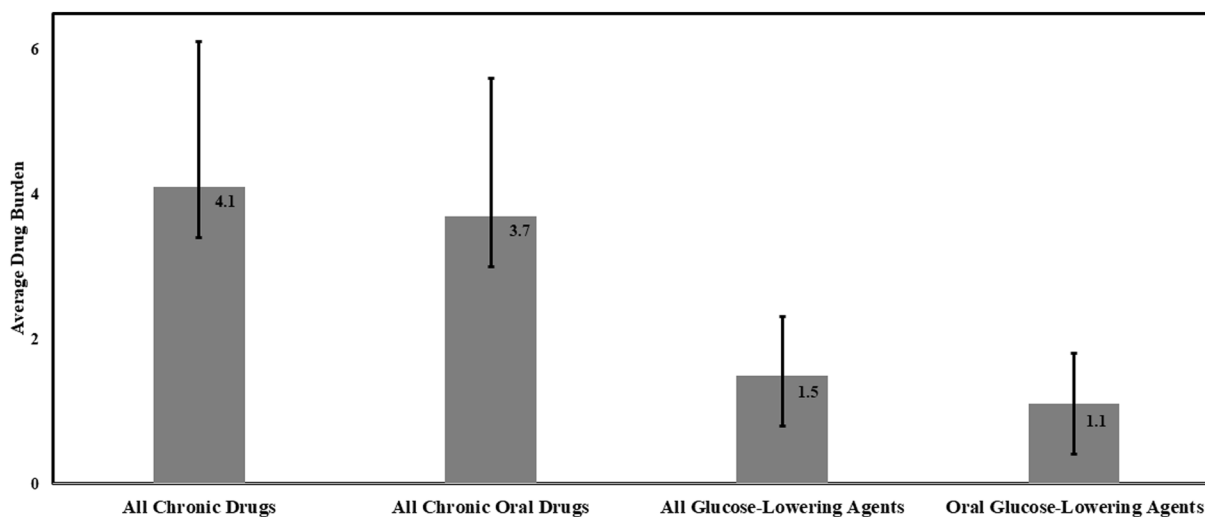


Fig. 1 Average daily medication burden for patients with type 2 diabetes. This figure illustrates the average number of medications prescribed in 2017 for all chronic medications with an oral route of administration, all glucose-lowering agents and glucose-lowering agents with an oral route of administration. See Supplementary Table 1 for a

complete listing of these medications. Mean \pm standard deviation (in error bars) reported in figure. Medians (interquartile range): all chronic medications = 3.9 (2.7–5.3); all chronic oral medications = 3.6 (2.4–4.9); all glucose-lowering agents = 1.2 (0.9–1.9); oral glucose-lowering agents = 1.0 (0.8–1.6)

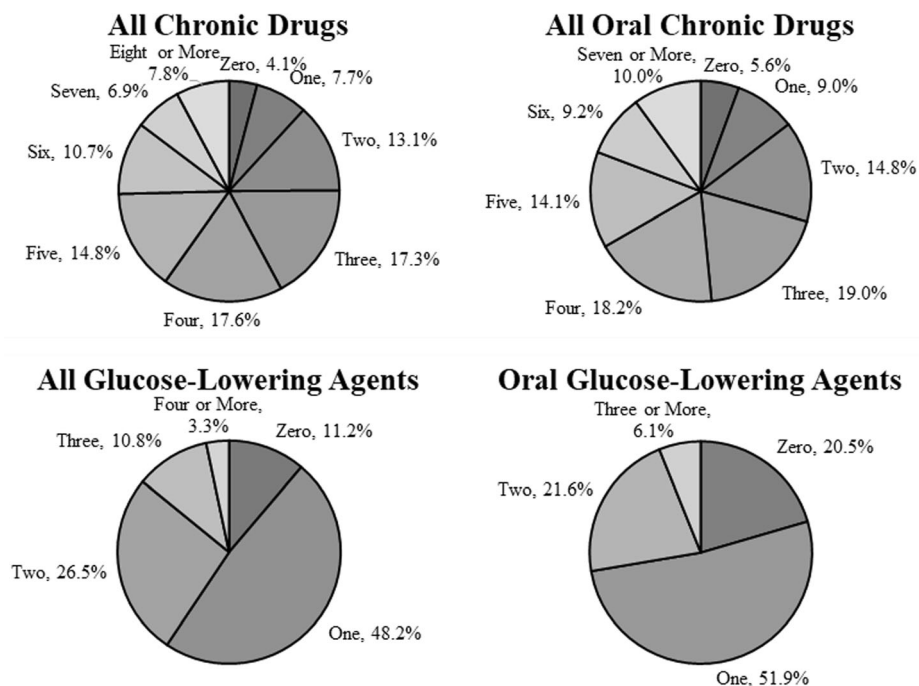


Fig. 2 Distribution of average days of medication use for patients with type 2 diabetes. Graphs represent the average percentage of days patients treated with number of medications of interest in 2017 for all chronic medications

with an oral route of administration, all glucose-lowering agents, and glucose-lowering agents with an oral route of administration. See Supplementary Table 1 for a complete listing of these medications

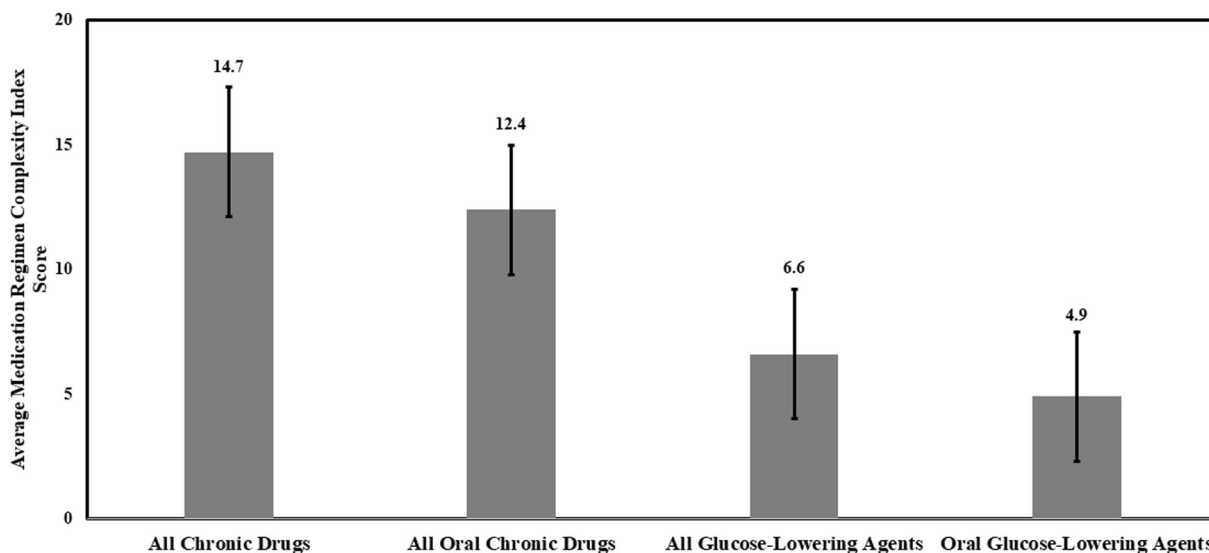


Fig. 3 Average medication regimen complexity index score for patients with type 2 diabetes. This figure illustrates the average Medication Regimen Complexity Index (MRCI) score in 2017 for all chronic medications, all chronic medications with an oral route of administration, all glucose-lowering agents, and glucose-lowering agents with an oral route of administration. See Supplementary Table 1

for a complete listing of these medications and Supplementary Table 5 for a description of how the MRCI is scored. Mean \pm standard deviation (in error bars) reported in figure. Medians (interquartile range): all chronic medications = 1.35 (9.1–19.0); all chronic oral medications = 11.5 (7.7–16.1); all glucose-lowering agents = 5.5 (3.7–8.7); oral glucose-lowering agents = 4.1 (3.0–6.4)

Table 2 Medication regimen complexity index: individual component scores

MRCI component	Oral GLAs		All GLAs		All orals		All medications	
	Mean ± SD	Median (IQ range)	Mean ± SD	Median (IQ range)	Mean ± SD	Median (IQ range)	Mean ± SD	Median (IQ range)
Dosage form	1.1 ± 0.7	1.0 (0.8–1.6)	2.2 ± 1.7	1.6 (1.0–3.0)	3.8 ± 1.9	3.6 (2.4–4.9)	5.1 ± 2.8	4.6 (3.0–6.6)
Dosing frequency	2.0 ± 1.3	1.9 (1.0–2.8)	2.4 ± 1.4	2.0 (1.4–3.2)	5.3 ± 2.8	4.9 (3.2–6.8)	5.8 ± 3.0	5.3 (3.6–7.4)
Additional directions	1.4 ± 1.1	1.0 (0.8–1.9)	1.9 ± 1.3	1.6 (0.9–2.7)	3.3 ± 2.2	2.9 (1.7–4.6)	3.8 ± 2.4	3.4 (2.0–5.2)

GLA glucose-lowering agent, IQ interquartile

patients with T2D was associated with poorer outcomes, including more chronic disease-related distress, lower self-efficacy, worse physical and mental health, greater financial struggles related to medical care, and poorer adherence to treatment [26, 27]. In addition, previous literature has shown that the use of multiple medications increases the risk of clinically important medication interactions [28], and research among older adults has found that the risk of inappropriate medication use increases along with the number of medications used [29].

The mean GLA-specific (6.6) and overall (14.7) MRCI scores in this study suggest that the typical T2D medication regimen is also complex. Previous research has reported that complex medication regimens are associated with negative health outcomes. For instance, a number of studies have found associations between increased medication treatment complexity and reduced adherence [30–32] as well as increased hospital admissions, hospital readmissions, and emergency room care [30]. Other research has demonstrated that patients with more complex medication treatment regimens tend to have worse glycemic control [31, 33].

Medication interactions are one of the commonest causes of medication errors [28], and some medication interactions can lead to serious unwanted outcomes or reduced therapeutic effects [34]. The observation that, on average, 23.3% of chronic medications included in the study had the potential to interact is consistent with research which has found that clinically significant medication interactions comprise an additional burden for patients with T2D, their physicians, and their pharmacists [28]. Finally, more than half of the chronic medication burden in this patient population was taken to treat comorbidities, and the presence of comorbidities has been previously shown to increase the risk of potentially inappropriate medication use [29].

In general, the total medication burden and complexity were lower in this study compared to previous research. For example, Libby et al. found an average MRCI score of 22.98 for individuals with diabetes [35], while this analysis found a mean MRCI of 14.7. Similarly, previous research found that the mean medication

burden after diagnosis of diabetes is 6.6 [36], while this study observed an average medication burden of 4.1 among patients identified with T2D. This discrepancy is consistent with the current analyses' conservative estimates of medication burden and complexity based upon the patient's actual filling of prescriptions. Specifically, the analyses focused only on chronic medications where prescriptions were filled by at least 2% of the population for at least 90 days in 2017. These criteria led to the omission of any medications, such as antibiotics, used for less than 3 months and any medications prescribed to relatively few individuals in the cohort. In addition, the analyses did not consider over-the-counter medications, vitamins, or supplements when examining patient medication regimens.

Generally consistent with other studies [9, 37], the average patient-level medication regimen was far more complex than the diabetes-specific regimen, a finding that reflects the large burden of chronic comorbidities associated with a diagnosis of T2D [4, 25]. This investigation found a mean MRCI for treatment of diabetes of 6.6 (median 5.5); previous research found a mean of approximately 6 for a cohort of patients with type 1 diabetes or T2D [35] and a median of 8.0 for patients with uncontrolled diabetes [38]. Notably, the prior research found that the disease-specific MRCI was higher for patients with diabetes compared to patients with hypertension, geriatric depression, and human immunodeficiency virus (HIV [35, 38]), reflecting the complexity associated with diabetes therapies, which may be administered in varying dosage forms and frequencies, and with additional directions.

The study had several strengths, including a larger patient population compared to previous research on medication regimen complexity [11, 31, 33, 35, 37, 38] and the focus on medication use over an entire calendar year. In addition, the study focused more broadly on the US population, rather than on unique US sub-populations or geographic regions [12, 35]. Moreover, the analyses were intentionally conservative, excluding medications for non-chronic conditions and medications used by less than 2% of the population. Treatment was

observed from multiple viewpoints, including the number of medications taken, the MRCI score, and the potential for medication interactions. Such a multiplicity of perspectives provides a more complete understanding of T2D treatment. Finally, the relatively recent data used in the analyses allows for a re-investigation of the use of T2D therapies, reflecting a recent significant increase in the number of medications available and the relatively new focus on the risk of cardiovascular disease associated with the use of GLAs [3].

The findings of this study should also be considered within the context of the limitations. The analyses focused on treated patients with T2D and hence did not represent the entire population of individuals with T2D. As a descriptive study which focused on treated patients with T2D, the analyses were unable to directly compare results across alternative cohorts of patients. Furthermore, the use of a claims database precluded capturing information such as patient socioeconomic status, education level, duration of diabetes, and glycemic control, which could help inform the study. In addition, given the use of claims data, medication use was proxied by prescription fill data, quantity of medication supplied, and days supplied. As such, the study was unable to identify whether patients actually took medication once a prescription was filled. In addition, such a proxy may not accurately capture variable dosing medications, such as insulin. While the focus on chronic medication provides a clearer picture of "typical" medication burden, the omission of acute medications may omit some important information. Finally, the analyses focused exclusively on chronic medications prescribed to at least 2% of our cohort and hence did not include all chronic medications used by patients with T2D.

CONCLUSIONS

On average, patients with T2D treated with GLAs used multiple medications, had a complex medication regimen, and were at noteworthy potential risk of medication interactions. These findings suggest that patients, practitioners,

pharmacists, and payers may benefit from interventions that are capable of decreasing medication burden, complexity, and/or adverse events related to the treatment of T2D. In addition, the results suggest the importance of selecting less complex interventions when multiple treatment options are available. Physicians and pharmacists should consider these issues when modifying patient medication regimens.

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Compliance with Ethics Guidelines. As a retrospective study which used de-identified data, the study did not seek institution review board approval. Permission to access data from IBM and Walters Kluwer was obtained via purchase of data licenses.

Data Availability. MarketScan[®] data and Facts and Comparisons[®] data used for this study are available via licensing agreements from IBM[®] and Wolters Kluwer, respectively. Data from DrugBank is freely available online (<https://www.drugbank.ca>).

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