A population-based analysis of anti-diabetic medications in four Canadian provinces: secular trends and prescribing patterns

Running head: Anti-diabetic drug prescription trends in Canada

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Key points:

- The Canadian Network for Observational Drug Effect Studies (CNODES) is useful for cross-jurisdictional drug utilization studies in Canada.
- Anti-diabetic medication prescription rates increased in the last two decades in most included provinces.
- Metformin increased in popularity since the 1990s and surpassed sulfonylureas as the most popular treatment option for type-2 diabetes in the early 2000s.
- Thiazolidinediones saw marked increases in popularity until 2007, when concerns about the safety of rosiglitazone motivated a shift towards other medications.
- Dipeptidyl peptidase-4 inhibitors have grown rapidly in popularity in recent years.

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ABSTRACT

Purpose: To use the Canadian Network for Observational Drug Effect Studies (CNODES) to describe drug utilization of anti-diabetic medications in four Canadian provinces.

Methods: Using data from CNODES, we constructed cohorts of patients with type 2 diabetes in four Canadian provinces (Manitoba, Ontario, Quebec, and Saskatchewan) who received their first-ever prescription for a non-insulin anti-diabetic medication during the study period, defined as the earliest date of data availability in each province (range: 1993–1998) to the latest date of the data extraction in each province (range: 2013–2014). Prescriptions rates were calculated for all prescriptions by class and described over time.

Results: Across provinces, we identified 650,830 patients who initiated anti-diabetic medications during the study period. In most provinces, the overall prescription rate of anti-diabetic medications increased during the last two decades. Metformin particularly increased in popularity, surpassing sulfonylureas in all provinces as the most widely prescribed anti-diabetic medication by the early 2000s. Thiazolidinediones grew in popularity from the onset of their availability until 2006–2007, at which point they rapidly declined. Dipeptidyl peptidase-4 inhibitors saw substantial growth in several provinces following their addition to provincial formularies in 2008–2012, while glucagon-like peptide-1 agonists experienced modest growth. Insulin prescription rates remained constant or steadily increased over the last two decades.

Conclusions: CNODES can be used for cross-jurisdictional drug utilization studies. In Canada, trends in anti-diabetic medication prescriptions followed changing guidelines reflecting up-to-date knowledge of drug effectiveness and safety.

INTRODUCTION

The number of anti-diabetic medications marketed for the treatment of type 2 diabetes mellitus (T2DM) has increased considerably over the last several decades, allowing for more personalized glycemic management according to patient comorbidities, drug tolerance, contraindications, and preference.[1-4] This increase and the evolution of clinical guidelines that consider the safety and efficacy of different anti-diabetic medications[5] and treatment regimens (*e.g.,* tight glycemic control)[6] have transformed prescribing patterns over time. In Canada, where 2.4 million persons live with T2DM,[7] trends in the utilization of anti-diabetic medications are not well described. Most studies documenting prescription patterns of these drugs have focused on a single province,[8-16] limiting their generalizability. Studies addressing nationwide trends in Canada are either at least 10 years out-of-date[17] or consider only one medication (rosiglitazone).[18] The Canadian Network for Observational Drug Effect Studies (CNODES),[19] a pan-Canadian network focused on drug safety and effectiveness, could serve as a useful resource for the Canada-wide study of anti-diabetic drug utilization. By using a distributed data network approach with CNODES, several provinces could be evaluated simultaneously, allowing for the assessment of provincial differences in drug utilization all while inferring nationwide trends. The objectives of this study were to demonstrate the utility of CNODES in evaluating Canadian drug utilization and to describe anti-diabetic drug utilization trends among T2DM patients in four Canadian provinces.

METHODS

We obtained data on dispensed anti-diabetic medication prescriptions from Manitoba (MB), Ontario (ON), Quebec (QC), and Saskatchewan (SK) using existing CNODES partnerships.[19] Prescription drug dispensing data from Canadian provinces are of high-quality, contain minimal

restrictions due to age or health care status, and have been widely applied to pharmacoepidemiologic research.[20-22]

In each province, we developed a cohort of patients who dispensed at least one non-insulin anti-diabetic medication. The cohort entry date for each patient was set to the date of their first dispensation of an anti-diabetic medication in the provincial database that was not insulin (to prevent the inclusion of patients with type 1 diabetes). We used the full duration of drug dispensing data available at each data site at the time of the analysis: January 1, 1996 to March 31, 2013 for MB; January 1, 1993 to March 31, 2013 for ON; January 1, 1998 to June 30, 2014 for QC; and January 1, 1997 to December 31, 2013 for SK. We excluded patients who met at least one of the following criteria: were <18 years old at cohort entry; had <1 year of database history prior to cohort entry; had inconsistent prescription information (*i.e.,* a prescription dispensed after the date of death or emigration, or a prescription dispensed outside of the range of data availability); received their first anti-diabetic prescription in a long-term care facility; had been previously treated with insulin or diagnosed with polycystic ovarian syndrome before cohort entry; and, had been diagnosed with gestational diabetes <1 year prior to cohort entry. In ON, the study population was limited to patients ≥65 years old, and in QC, the study cohort included patients in any of the following groups: those ≥65 years old, those on social insurance, and those not covered by private insurance (*e.g.,* the self-employed). Patients were followed from their cohort entry date until the end of data availability at each province or until withdrawal from the database due to death, emigration, or a change in prescription drug coverage.

Individual medications were organized into their respective classes: metformin, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, insulin, and all others. Combination formulations involving multiple classes

(*e.g.,* metformin + rosiglitazone) were treated as separate prescriptions for the constituent classes. We calculated annual prescription rates of drug classes for each study province as prescriptions per person-year. We derived prescriptions per person-year as the sum of all prescriptions (not just the first-ever prescription for an anti-diabetic medication) during the analysis year divided by the person-years of follow-up for that year. Patients only contributed follow-up time between cohort entry and cohort exit, as defined above.

RESULTS

We identified a total of 650,830 patients receiving a new, non-insulin anti-diabetic medication, of which the greatest number came from ON (n=279,476), followed by QC (n=212,402), MB (n=81,399), and SK (n=77,553). A total of 4,255,813 person-years of follow-up and 48,301,445 prescriptions for anti-diabetic medications were accrued across provinces.

Prescription rates for anti-diabetic medications decreased briefly in the mid- to late-1990s and increased steadily thereafter for all provinces except SK, where overall prescription rates declined steadily throughout study follow-up (Figures S1–S4). Metformin and sulfonylureas consistently had the highest prescription rates over the last two decades (Figures 1–4). In the 1990s, sulfonylureas were prescribed at greater rates than metformin. However, from the late 1990s to the early 2000s, metformin prescription rates increased as sulfonylurea prescription rates declined. By 2003, metformin surpassed sulfonylureas in all participating provinces. In the mid- to late-2000s, the prescription rates of metformin and sulfonylureas were constant relative to the sum of all anti-diabetic prescriptions (Figures S5–S8).

TZD prescription rates increased quickly across study sites in the early 2000s and reached their maxima in 2006–2007 before declining quickly (Figures 1–4). More recent TZD prescription rates

were considerably lower than peak rates. For example, in QC, TZDs peaked at 1.2 prescriptions/person-year in 2007, but lowered to 0.2 prescriptions/person-year in 2014. Prescription rates for insulin remained constant or steadily increased in all provinces. For example, prescriptions for insulin in SK grew from 0.2 prescriptions/person-year in 1997 to 1.3 prescriptions/person-year in 2013, surpassing sulfonylureas in the process. Starting as early as 2008, prescriptions rates for DPP-4 inhibitors grew rapidly, particularly in QC and ON. Though GLP-1 agonists have been available in two study provinces (MB, QC) since as early as 2010, their use only slightly increased over the study period, remaining below 0.2 prescriptions/person-year. Other drugs such as meglitinides, alpha-glucosidase inhibitors, or sodium-glucose cotransporter 2 inhibitors were prescribed at relatively low rates throughout the study period.

DISCUSSION

We observed secular increases in total anti-diabetic medication prescription rates in all study provinces but SK. Higher prescription rates are consistent with more recent guidelines that recommend two- or three-medication combinations for patients who fail to reach target HbA1c levels.[1-4,23-25] The push for more aggressive control of HbA1c levels in the last two decades to reduce the risk of cardiovascular disease and other complications[26-28] likely also contributed to the rise in prescription rates, though the benefit of aggressive glycemic control is subject to debate,[6,29] which may impact future prescription patterns.

We note here that another possible explanation for the observed increase in prescription rates is the changing makeup of the study cohort over time. In the first year of the study period at each site, the study cohort consisted of patients newly treated for diabetes (*i.e.,* incident users) within that year. These patients remained in the cohort (*i.e.,* becoming prevalent users), with their anti-diabetic regimens changing over time, while incident users continued to enter the cohort. Thus,

the cohort increasingly consisted of prevalent users more likely to be older and on later lines of therapy. This feature of the study cohort may partially explain the observed trend towards higher anti-diabetic prescription rates over time as patients are increasingly likely to take multiple anti-diabetic medications after the first line. Similarly, this feature of the study cohort likely explains the rapid decrease in sulfonylurea prescription volume observed in some databases following the first year of the study period, reflecting the change in therapy for incident users who failed sulfonylureas as first line. We assume the increase in the use of insulin over time also predominately relates to the changing makeup of the study cohort and not physician preference.

The substantial growth in metformin's popularity since the late 1990s is likely attributable to its perceived safety and lack of effect on weight gain as a monotherapy[30] or add-on therapy to insulin.[31] These beneficial aspects of metformin therapy ultimately motivated the Canadian Diabetes Association to recommend it as the primary monotherapy for incident T2DM in 2008.[32] Previous guidelines recommended sulfonylureas;[26] the shift from sulfonylureas to metformin in our databases supports adherence to clinical guidelines. Despite their decrease in popularity, sulfonylureas remained generally more popular than other medications, likely due to the common clinical practice[33] of prescribing sulfonylureas as the preferred second-line treatment to patients who fail metformin monotherapy. In addition, sulfonylureas are relatively inexpensive, and so were required before newer agents in most provincial formularies.

TZDs were prescribed at increasing rates through the mid-2000s in the study databases. During this time period, TZDs such as pioglitazone and rosiglitazone were considered to be efficacious and safe as mono- or combination therapies[34-36] and were thought to possess beneficial cardiovascular effects.[34,37,38] The observed decrease in TZD prescriptions occurred shortly after the publication in 2007 of a meta-analysis by Nissen and colleagues[39] associating rosiglitazone use

with increased risk of myocardial infarction and cardiovascular mortality. Drug utilization studies have thoroughly documented the decrease in TZD prescription rates in Ontario,[9,14,40] British Columbia,[13] and Canada-wide.[18] Many of these studies[9,13,14,40] further observed that pioglitazone grew in popularity following the Nissen publication, suggesting physicians were skeptical of a class-wide TZD effect.[37] Still, overall TZD prescription rates have declined since 2007. Concerns of an association between pioglitazone and bladder cancer that subsequently emerged may have contributed to physicians' continued reluctance to prescribe this drug class.[41]

The increasing popularity of insulin at several sites (most notably SK and MB) may result from a growing willingness among clinicians to commence early insulin therapy. Historical guidelines support this narrative: in 1998, the Canadian Diabetes Association recommended insulin therapy after other oral mono- and combination therapies,[42] whereas more recent recommendations consider insulin as a primary monotherapy (in some patients) or early combination treatment.[1,26,32] The recent availability of long-acting insulin analogs such as insulin glargine and insulin detemir likely added to the rise of insulin.

DPP-4 inhibitors entered the Canadian market in 2008 and increased in popularity because of their low risk of hypoglycemia, weight gain, and other side-effects.[23,43,44] GLP-1 agonists, on the other hand, have experienced slow growth since 2010 in the provinces where they are approved, consistent with their relatively high cost and risk of gastric side effects when compared to DPP-4 inhibitors.[43] Formulary restrictions for DPP-4 inhibitors and GLP-1 agonists may have slowed the rate of growth of both these classes, as they are not easily reimbursed. Recent reports on the potential for DPP-4 inhibitors to provoke heart failure[21,45,46] and the potential benefit of GLP-1 agonists on cardiovascular disease[46,47] may alter the observed preference for DPP-4 inhibitors relative to GLP-1 agonists in the future. Sodium-glucose co-transporter 2 inhibitors may also

increase in popularity relative to these incretin-based therapies because of their likely cardioprotective effects.[46,48,49]

Our study has several strengths. The use of CNODES, which contains population-wide healthcare data with few restrictions for seven Canadian provinces, limited selection bias. Our study had lengthy follow-up durations (up to 20 years), enabling the examination of secular trends that are more compatible with the timelines of research and guideline development than previous reports on this topic. Finally, the separate analysis of multiple provincial databases using a distributed protocol respected data custodian privacy requirements while providing a multi-jurisdictional view of prescribing practices in Canada.

Our study also has some potential limitations. The lack of data from 2014 onwards prevented the assessment of the uptake of sodium-glucose co-transporter 2 inhibitors and the impact of large cardiovascular outcome trials on treatment patterns. Our study was additionally limited to data from four provinces, though future CNODES drug utilization studies could also include data from three additional provinces (British Columbia, Alberta, and Nova Scotia), as well as data from the United States (via Truven's MarketScan payer claims database) and the United Kingdom (via the Clinical Practice Research Datalink, an electronic health record database). As another limitation, we did not consider individual patient characteristics in this analysis, and some observed differences between provinces may be explained by patient characteristics (*e.g.,* because age was restricted to those aged 65 or older in ON and those aged 65 or older, those receiving social assistance, and those not covered by other drug plans in QC). However, provinces that capture subsets of the population (ON, QC) had similar trends to those with full population data capture (MB, SK), suggesting selection bias was limited. Changing patient characteristics over time may also have impacted observed secular trends, particularly the change in the ratio of incident to

prevalent users. For instance, sulfonylureas may have decreased in popularity in early follow-up years and insulin may have become more popular over time because the study cohorts increasingly contained prevalent users with long-term T2DM. By excluding patients with insulin as a first-line therapy, we may have inadvertently removed from study some patients with type 2 diabetes whose earlier therapies were not captured (e.g., due to left truncation or the use of private insurance). Insulin use may be underestimated by the exclusion of these patients. Another limitation was our focus on prescription counts, and not dose or duration/quantity dispensed. As a result, some apparent secular changes or cross-jurisdiction differences may not actually reflect patient management. Finally, the provincial databases only captured prescriptions filled, not administered, so the reported prescription rates reflect both patient and physician behavior.

CONCLUSIONS

The use of the distributed data drug safety network CNODES allowed for the cross-jurisdiction study of anti-diabetic drug utilization in Canada. Through its application of a common protocol in a distributed data setting, CNODES can provide a pan-Canadian view of treatment practices and trends, while ensuring a similar methodological approach across provinces and respecting provincial data privacy requirements.

Anti-diabetic medication prescribing has increased in Canada the last two decades in accordance with guidelines that favor tight glycemic control and endorse a variety of combination therapies. Per more recent guidelines, metformin has surpassed sulfonylureas as the primary treatment option for T2DM and insulin has become a more commonly prescribed therapy. TZDs saw rapid uptake, followed by a sharp decrease in prescriptions following emergent safety concerns. New drug classes such as DPP-4 inhibitors and GLP-1 agonists have been increasingly prescribed by physicians to the extent that they are considered safe and cost-effective. The future of these

relatively new drugs and combinations will likely favor GLP-1 agonists and sodium-glucose co-transporter 2 inhibitors based on recent evidence of their cardiovascular safety.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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FIGURE LEGENDS

Figure 1. **Prescription rates of anti-diabetic medication classes for the treatment of type 2 diabetes in the province of Ontario between January 1, 1993 and March 31, 2013**

TZDs and DPP-4 inhibitors refer to thiazolidinediones and dipeptidyl peptidase-4 inhibitors, respectively. Formulary restrictions in Ontario prevented the reimbursement of glucagon-like peptide-1 (GLP-1) agonists.[50]

Figure 2. **Prescription rates of anti-diabetic medication classes for the treatment of type 2 diabetes in the province of Manitoba between January 1, 1996 and March 31, 2013**

TZDs, DPP-4 inhibitors, and GLP-1 agonists refer to thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 agonists, respectively.

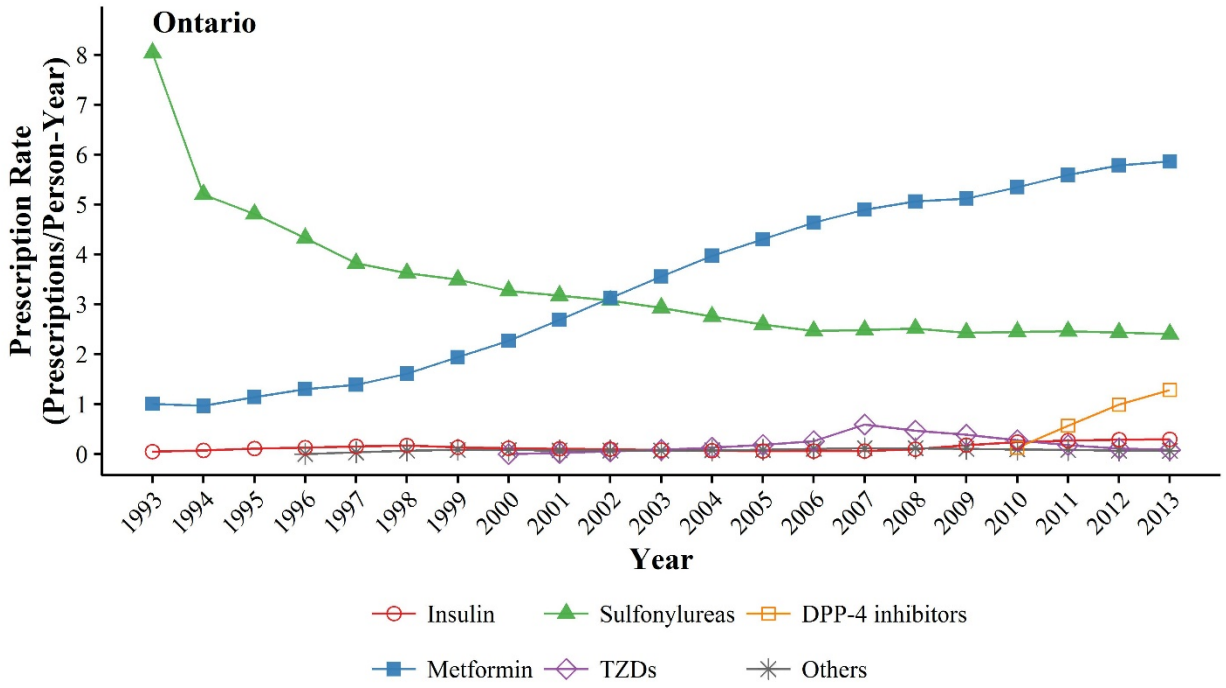
Figure 3. **Prescription rates of anti-diabetic medication classes for the treatment of type 2 diabetes in the province of Saskatchewan between January 1, 1997 and December 31, 2013**

TZDs and DPP-4 inhibitors refer to thiazolidinediones and dipeptidyl peptidase-4 inhibitors, respectively. Formulary restrictions in Saskatchewan prevented the reimbursement of glucagon-like peptide-1 (GLP-1) agonists.[51]

Figure 4. **Prescription rates of anti-diabetic medication classes for the treatment of type 2 diabetes in the province of Quebec between January 1, 1998 and June 30, 2014**

TZDs, DPP-4 inhibitors, and GLP-1 agonists refer to thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 agonists, respectively.

Figure 1


Ontario
Prescription Rate
(Prescriptions/Person-Year)
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3
4
5
6
7
8
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Year
Insulin
Sulfonylureas
DPP-4 inhibitors
Metformin
TZDs
Others

Figure 2

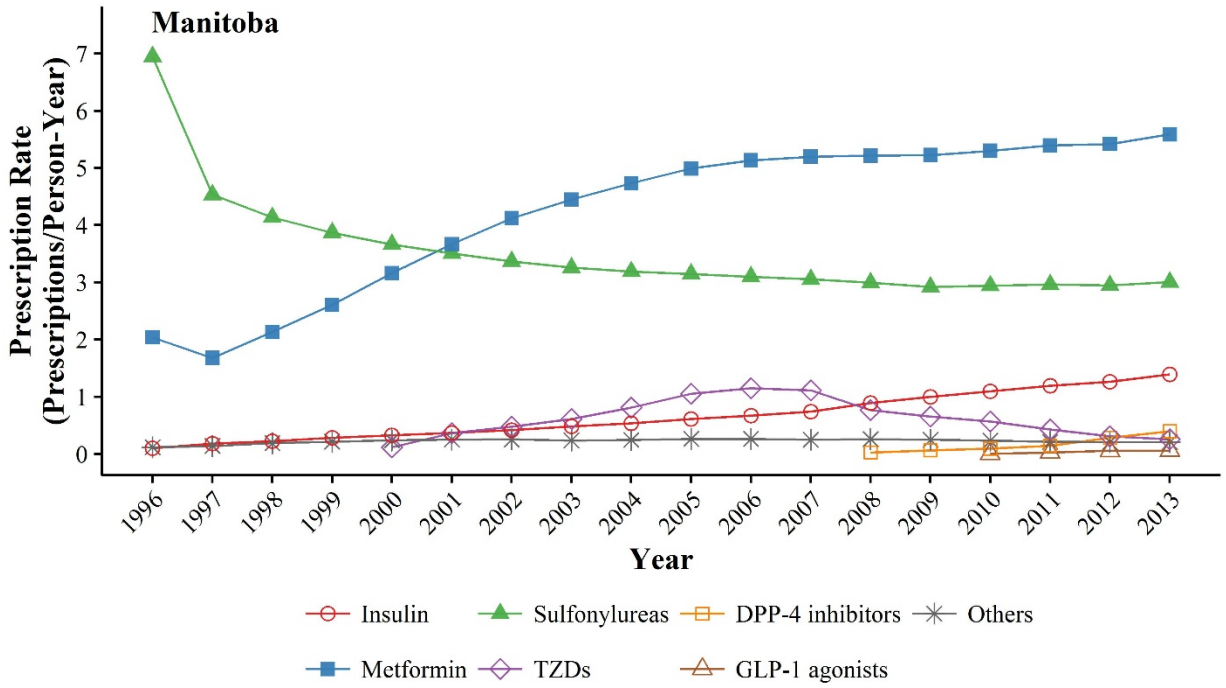

Manitoba
Prescription Rate
(Prescriptions/Person-Year)
0
1
2
3
4
5
6
7
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Year
Insulin
Sulfonylureas
DPP-4 inhibitors
Others
Metformin
TZDs
GLP-1 agonists

Figure 3

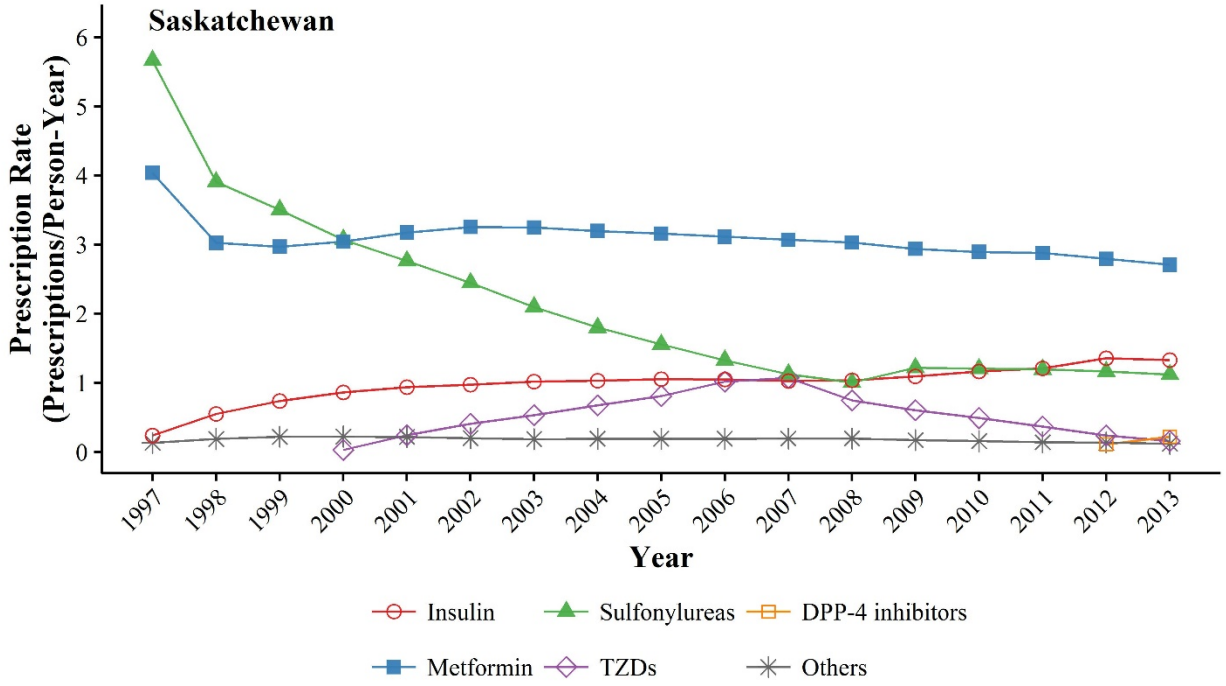
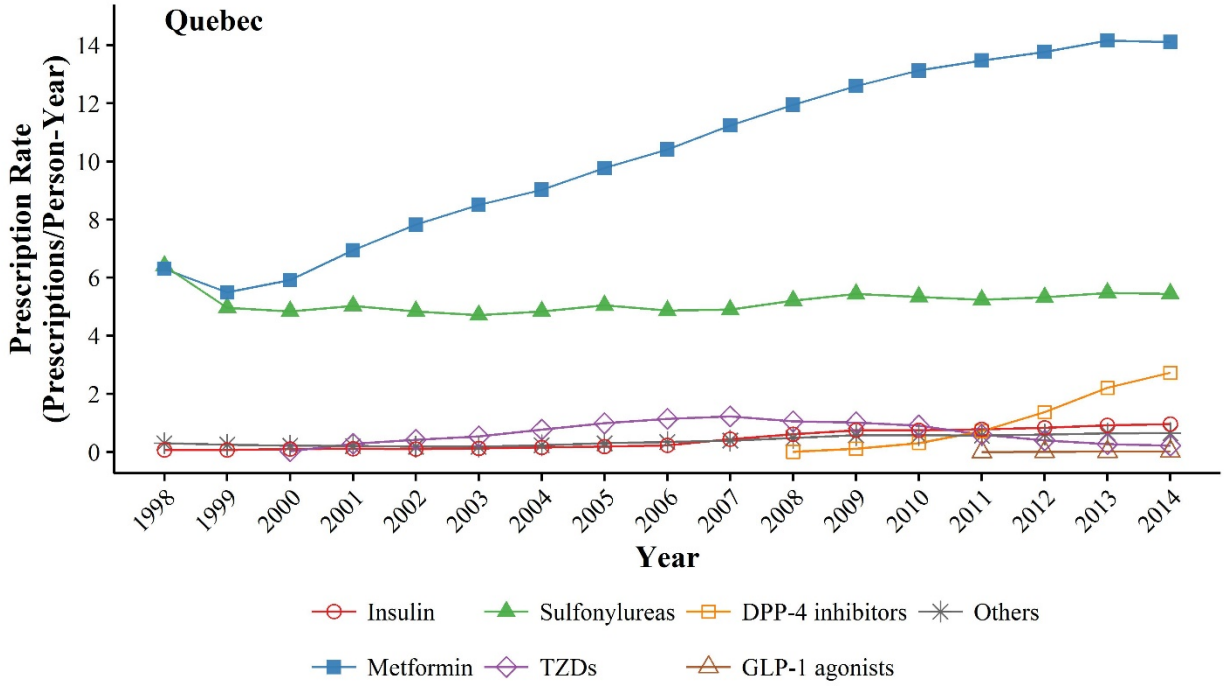

Saskatchewan
Prescription Rate
(Prescriptions/Person-Year)
0
1
2
3
4
5
6
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Year
Insulin
Sulfonylureas
DPP-4 inhibitors
Metformin
TZDs
Others

Figure 4


Quebec
Prescription Rate
(Prescriptions/Person-Year)
0
2
4
6
8
10
12
14
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year
Insulin
Sulfonylureas
DPP-4 inhibitors
Others
Metformin
TZDs
GLP-1 agonists