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Rurality is associated with lower likelihood of dipeptidyl peptidase 4 inhibitor use for treatment intensification

Danielle K. Nagy [a], Lauren C. Bresee [b], Dean T. Eurich [c], Scot H. Simpson [d,*]

[a] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, 2-35, Medical Sciences Building, 8613 – 114 St., Edmonton, Alberta T6G1C9, Canada
[b] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta T2N4N1, Canada
[c] School of Public Health, University of Alberta, 2-040F Li Ka Shing Centre For Research, 11203 – 87 Ave NW, Edmonton, Alberta T6G2H5, Canada
[d] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, 2-020C, Katz Group Centre for Research, 11315 – 87 Ave NW, Edmonton, Alberta T6G2H5, Canada

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ABSTRACT

Background: Antihyperglycemic drug utilization studies are conducted frequently and describe the uptake of new drug therapies across may jurisdictions. An increasingly important, yet often absent, aspect of these studies is the impact of rurality on drug utilization.
Objective(s): The objective of this study was to explore the association between place of residence (rural, urban, metropolitan) and the use of dipeptidyl peptidase 4 inhibitors (DPP-4i) for first treatment intensification of type 2 diabetes.
Methods: A retrospective cohort study was conducted from April 1, 2008 to March 31, 2019 of new metformin users. A multivariable logistic regression analysis was performed to determine the association between place of residence (using postal codes) and likelihood of DPP-4i dispensing.
Results: After adjusting for confounders, analysis revealed that rural-dwellers are less likely to have a DPP-4i dispensed, compared with metropolitan-dwellers (aOR:0.64; 95%CI:0.61–0.67) and over-time, the uptake in rural areas was slower.
Conclusions: This study demonstrates that rurality can have an impact on drug therapy decisions at first treatment intensification, with respect to the utilization of new therapies.

1. Introduction

Many have described trends in the dispensing of antihyperglycemic therapies globally, however, few consider the impact of rurality.[1–3] Some of the earliest literature in this area suggests that rurality is associated with low achievement of glycated hemoglobin A1C, blood pressure, and cholesterol targets, underuse of aspirin therapy, and lower use of combination drug therapy to treat type 2 diabetes and hypertension when targets are not being met.[4–6] Others have identified rural and remote dwellers as 2 to 3 times more likely to experience a hospitalization for hypo or hyperglycemia as an acute complication of diabetes.[7] More recently, it has been reported that individuals living with type 2 diabetes and in rural areas are more likely to be dispensed a sulfonylurea at first treatment intensification (FTI), compared to their metropolitan-dwelling counterparts.[8] Considering the increased use of sulfonylureas in rural areas and lower use of combination therapies, the question remains whether residence impacts the uptake of newer drug therapies such as dipeptidyl peptidase 4 inhibitors (DPP-4i).

The first DPP-4i was approved for use by Health Canada in 2008 and was recommended at treatment intensification for being weight neutral and having a low risk of hypoglycemia beginning in the 2008 Canadian Diabetes Association Clinical Practice Guidelines.[9–11] In the Canadian province of Alberta, (population: 4 million people) DPP-4i are eligible for publicly funded provincial drug insurance coverage if an individual previously trialed metformin, a sulfonylurea, and where insulin is not an option.[12,13]

Taken together, the reports of differential diabetes management according to residence, despite having access to the same provincial drug availability, publicly funded provincial drug insurance programs, and national clinical practice guidelines, is concerning. The objective of this study was to further this line of research by examining the uptake of DPP-4i along the rural-urban continuum and since its approval for use.

* Corresponding author.
E-mail address: scot@ualberta.ca (S.H. Simpson).

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The primary hypothesis of this research was that uptake will be slower in rural areas and lag behind urban and metropolitan utilization.

2. Methods

This retrospective cohort study analyzed administrative health records of adult new metformin users in Alberta between April 1, 2008 and March 31, 2019. A new metformin user was defined as an individual age 18 years or older with no history of antihyperglycemic drug therapy in the past 12 months, and their first instance of antihyperglycemic drug therapy being metformin.[14] Additionally, individuals were excluded if they were diagnosed with gestational diabetes (International Classification of Diseases-10 code O24.xx) in the 9 months before FTI or at all during follow up.[15] Individuals were followed until they experienced the outcome of interest, a pharmacy dispensing record for FTI with a DPP-4i either alone or in combination with other therapies. At the time an individual received FTI, their postal code was used to categorize their place of residence as rural, urban, or metropolitan, based on Alberta Health's geographic boundaries.[16,17]

Multivariable logistic regression was used to determine whether there was an association between place of residence and FTI with a DPP-4i. Several baseline characteristics were adjusted for in the model to control for confounding including age, sex, time since first metformin was dispensed, healthcare utilization, and diabetes complications based on the available data and other literature (Table 1).[18–21] Additionally, a count of the unique number of prescription drug therapies dispensed in the baseline year prior to first metformin was included in the model to control for possible confounding related to the burden of comorbid conditions and polypharmacy. Knowing that laboratory data should guide clinical decision making, a subgroup analysis was performed for individuals with laboratory data available (estimated glomerular filtration rate or creatinine clearance and glycated hemoglobin HbA1c). As this research is an extension of previously reported findings, these methods have been further detailed elsewhere.[8]

All analyses were performed in STATA version 16.1. The University of Alberta Research Ethics Board approved this study (Pro00066037).

3. Results

Of 171,759 adult new metformin users, 66,064 received treatment intensification and 15,467 (23%) were intensified with a DPP-4i. Baseline demographics are described in Table 1. At the beginning of the observation period, the proportion of DPP-4i dispensed according to place of residence was similar (7% metropolitan, 6% urban, 5% rural) -see Fig. 1. However, year over year, the gap widened between rural and metropolitan/urban to a maximum 10% difference in 2014/15 (32% metropolitan, 27% urban, 22% rural). Thereafter, DPP-4i dispensing dipped slightly in all locations (after the 2014/15 fiscal year) which corresponds with the market approval of SGLT2i, and then level-off.[9]

After adjusting for potential confounders, individuals living in rural areas were 36% less likely to receive a DPP-4i at FTI, compared with individuals living in metropolitan areas (aOR: 0.64; 95% CI: 0.61–0.67). This remained unchanged in the subgroup of those with laboratory data available (aOR: 0.64; 95% CI: 0.59–0.69). Of note, no interaction between sex and place of residence was found in these models.

4. Discussion

Key findings demonstrate that not only are individuals living with type 2 diabetes in rural areas less likely to have a DPP-4i dispensed at FTI, but also year over year the uptake of this drug class in rural areas substantially lags behind urban and metropolitan locations. Healthcare disparities among rural-dwellers in Alberta has been described in the literature for decades and these results demonstrate that over time, not much has changed.[4–6,8,22] Despite programs to attract healthcare professionals to rural areas to improve healthcare access, different

Table 1
Baseline demographics across the rural-urban continuum.

	Metropolitan (n = 41,646)	Urban (n = 6800)	Rural (n = 17,638)	Standardized Difference*
Fiscal Year, n (%)[a]				0.03 (M-U)
2009/2010	3129 (7.5)	390 (5.7)	1159 (6.6)	
2010/2011	3413 (8.2)	511 (7.5)	1475 (8.4)	
2011/2012	3647 (8.8)	594 (8.7)	1520 (8.6)	
2012/2013	3694 (8.9)	731 (10.8)	1636 (9.3)	
2013/2014	4169 (10.0)	648 (9.5)	1811 (10.3)	
2014/2015	4810 (11.5)	809 (11.9)	2065 (11.7)	
2015/2016	5770 (13.9)	974 (14.3)	2454 (13.9)	
2016/2017	6252 (15.0)	1103 (16.2)	2687 (15.2)	
2017/2018	6762 (16.2)	1040 (15.3)	2831 (16.0)	
Age (years), mean (SD)	55.3 (12.5)	53.7 (12.6)	56.0 (13.0)	0.18 (U-R)
Male, n (%)	25,593 (61.5)	4360 (64.1)	10,812 (61.3)	0.06 (U-R)
Time since first metformin (years), mean (SD)	1.5 (1.9)	1.5 (1.9)	1.6 (1.9)	0.05 (U-R)
Number of physician visits [b], n (%)				0.18 (M-R)
0–6	8627 (20.7)	1785 (26.3)	4850 (27.5)	
7–12	10,781 (25.9)	1850 (27.2)	4704 (26.7)	
13–24	11,721 (28.1)	1736 (25.5)	4479 (25.4)	
≥ 25	10,517 (25.3)	1429 (21.0)	3605 (20.4)	
Hospitalization [b], n (%)	5227 (12.6)	1032 (15.2)	3350 (19.0)	0.18 (M-R)
Number of unique prescriptions [b], n (%)				0.17 (M-R)
0–2	13,243 (31.8)	1926 (28.3)	4533 (25.7)	
3–5	11,248 (27.0)	1826 (26.9)	4527 (25.7)	
6–8	7714 (18.5)	1328 (19.5)	3458 (19.6)	
≥ 9	9441 (22.7)	1720 (25.3)	5120 (29.0)	
Diabetes Complications, n (%)				
Retinopathy	9524 (22.9)	1604 (23.6)	2983 (16.9)	0.17 (U-R)
Nephropathy	2027 (4.9)	329 (4.8)	950 (5.4)	0.02 (U-R)
Neuropathy	4233 (10.2)	789 (11.6)	2196 (12.5)	0.07 (M-R)
Ischemic Heart Disease	10,743 (25.8)	1569 (23.1)	4710 (26.7)	0.08 (U-R)
Prior Stroke	1731 (4.2)	197 (2.9)	704 (4.0)	0.07 (M-U)
Peripheral Vascular Disease	1724 (4.1)	327 (4.8)	1102 (6.2)	0.10 (M-R)
Hyperlipidemia	18,632 (44.7)	2643 (38.9)	7275 (41.2)	0.12 (M-U)
Diabetic Foot Infection	2748 (6.6)	545 (8.0)	2155 (12.2)	0.19 (M-R)
Prior Amputation	237 (0.6)	41 (0.6)	120 (0.7)	0.01 (M-R)
Dental Complications	3659 (8.8)	733 (10.8)	2436 (13.8)	0.16 (M-R)

(*continued on next page*)

Table 1 (*continued*)

	Metropolitan (n = 41,646)	Urban (n = 6800)	Rural (n = 17,638)	Standardized Difference*
Hypoglycemia	724 (1.7)	179 (2.6)	484 (2.7)	0.07 (M-R)
Number of other chronic conditions[c], n (%)				0.14 (M-R)
0–1	6644 (16.0)	1040 (15.3)	2337 (13.2)	
2	11,618 (27.9)	1711 (25.2)	4285 (24.3)	
3–4	15,221 (36.5)	2563 (37.7)	6815 (38.6)	
≥ 5	8163 (19.6)	1486 (21.9)	4201 (23.8)	

* Standardized difference is both the absolute value and maximum among the 3 pairwise comparisons.

[a] Percentage by fiscal year (Alberta Health fiscal year runs April to March), M-U = metropolitan-urban comparison, SD = standard deviation, U-R = urban-rural comparison, M-R = metropolitan-rural comparison.

[b] In the year prior to first metformin.

[c] As listed in Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998;36(1):8–27.

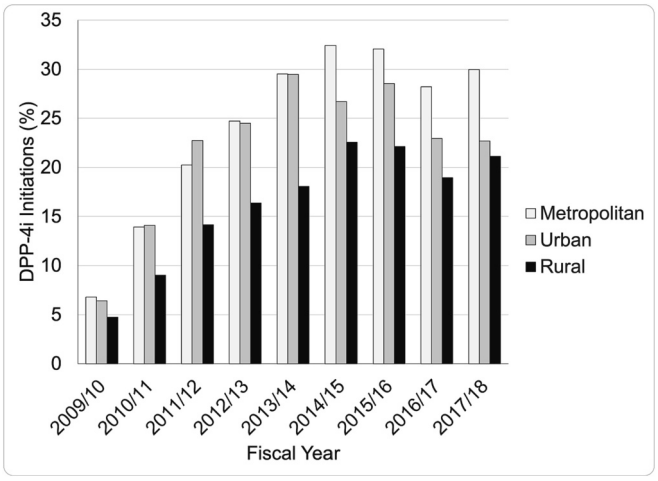

Fig. 1. Dipeptidyl peptidase 4 inhibitor (DPP-4i) dispensations over time across the rural-urban continuum.
White bars = metropolitan; grey bars = urban; black bars = rural.

management practices still exist across the rural-urban continuum, as evidenced by this research.[23,24] Of particular concern however, is the delayed incorporation of new drug therapies into practice, as seen with DPP-4is.

While it is likely that the limited use of DPP-4is in rural areas is a result of the sustained use of sulfonylureas in these locations, as previously reported, justification for these clinical decisions remains unknown and is beyond the scope of this study.[8] Current literature is also sparse in identifying patient and clinician factors underpinning differential processes of care and management strategies. Some speculate a difference in patient expectations of the healthcare system based on where they live, or differences in the use or methods of engagement with clinical practice guidelines and continuing education initiatives based on where a clinician practices.[25–29] Considering that individuals with publicly funded provincial drug insurance require a trial of metformin and a sulfonylurea before a DPP-4i will be covered, this may partly explain these findings however, as previously described, the largest caseloads of individuals with these drug insurance plans reside in metropolitan locations.[8] In light of this, these findings are likely a result of multifaceted patient and clinician factors which require further investigation.

Acknowledging limitations of this work include possible residual confounding from unmeasured factors which may impact drug therapy utilization such as drug insurance coverage, income level, education level, and medication taking beliefs. However, these data are not routinely collected by Alberta Health or made available in their administrative datasets.[30] Despite this, the study is strengthened by the large sample size, which represents all Albertans with type 2 diabetes when FTI is required. Additionally, the lengthy observation window enables not only trends over time, but also analysis beginning when DPP-4is were first available for use in Canada.

5. Conclusion

This study provides further evidence of differential type 2 diabetes care received among those living in rural locations, with a particular focus on the uptake of new drug therapies. A necessary next step in this line of research, which is currently underway, is to determine whether the differences in the management of type 2 diabetes along the rural-urban continuum results in jeopardized health outcomes, namely risk of microvascular and macrovascular complications.

CRediT authorship contribution statement

Danielle K. Nagy: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Lauren C. Bresee:** Writing – review & editing, Methodology, Conceptualization. **Dean T. Eurich:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Scot H. Simpson:** Writing – review & editing, Project administration, Methodology, Data curation, Conceptualization.

Declaration of competing interest

No potential conflicts of interest relevant to this article were reported. S.H.S. is supported as the Chair in Patient Health Management, jointly held by the Faculty of Pharmacy and Pharmaceutical Sciences and Faculty of Medicine and Dentistry, University of Alberta. This study is based in part on data provided by Alberta Health. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta. Neither the Government of Alberta nor Alberta Health express any opinion in relation to this study.

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