SHAPING WITH DATA: USING PHARMACOEPIDEMIOLOGY TO SHAPE PHARMACEUTICAL POLICY AND CLINICAL DECISION-MAKING

EDITED BY: Mina Tadrous and Andrea Burden
PUBLISHED IN: Frontiers in Pharmacology

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-83250-591-5
DOI 10.3389/978-2-83250-591-5

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

SHAPING WITH DATA: USING PHARMACOEPIDEMIOLOGY TO SHAPE PHARMACEUTICAL POLICY AND CLINICAL DECISION-MAKING

Topic Editors:
Mina Tadrous, Women's College Hospital, Canada
Andrea Burden, ETH Zürich, Switzerland

Citation: Tadrous, M., Burden, A., eds. (2022). Shaping With Data: Using Pharmacoepidemiology to Shape Pharmaceutical Policy and Clinical Decision-Making. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83250-591-5

Table of Contents

frontiers | Frontiers in Pharmacology

TYPE Editorial
PUBLISHED 12 October 2022
DOI 10.3389/fphar.2022.1023304

OPEN ACCESS

EDITED AND REVIEWED BY
Heike Wulff,
University of California, Davis,
United States

*CORRESPONDENCE
Mina Tadrous,
mina.tadrous@utoronto.ca

SPECIALTY SECTION
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

RECEIVED 19 August 2022
ACCEPTED 29 September 2022
PUBLISHED 12 October 2022

CITATION
Tadrous M and Burden A (2022), Editorial: Shaping with data: Using pharmacoepidemiology to shape pharmaceutical policy and clinical decision-making. *Front. Pharmacol.* 13:1023304. doi: 10.3389/fphar.2022.1023304

Editorial: Shaping with data: Using pharmacoepidemiology to shape pharmaceutical policy and clinical decision-making

Mina Tadrous[1]* and Andrea Burden[2]

[1]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada, [2]Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, ETH Zurich, Zurich, Switzerland

KEYWORDS

big data, pharmacoepidaemiology, drug policy, pharmaceutical services, observational studies

Editorial on the Research Topic
Shaping with data: Using pharmacoepidemiology to shape pharmaceutical policy and clinical decision-making

Policymakers around the world are grappling with an influx of rapidly changing science and new treatments in the area of medications and health technology. Much of their decisions have historically relied on randomized controlled trial (RCT) data for drug assessments. Over the past decade, it has become important for many decision-makers to realize that the RCT design may not reflect real-life clinical practice as the trial populations may exclude important patients seen in clinical practice. More importantly, the RCT is unable to answer questions related to rare adverse events, optimal use, and access. Therefore, the use of real-world data in the field of pharmacoepidemiology has, in many cases, stepped up to help policymakers fill these gaps. In this special topic, we aimed to gather a global cross-section of various papers that showcase the power of pharmacoepidemiology in helping shape policy and clinical practice.

We set out to cover the many areas that pharmacoepidemiology can be used to shape and inform policymakers, including understanding beneficial and adverse drug effects of medications, drug utilization, real-world effectiveness, clinical effects of drug-drug interactions, effects of medication non-adherence, and the impact of policy changes on drug utilization. We were able to do just that and covered many of these topic areas. Excitingly we received work from over eight different countries, each leveraging unique data sources and study designs that truly highlight the breadth of work that can happen in this field. Most importantly we received work that showcased the ability for pharmacoepidemiology to be used in studying drug safety, policy, and clinically relevant questions.

Specifically, we included a number of exciting papers on the safety of drugs with important clinical applications in the area of anticoagulants (Perreault et al.), drug-drug interactions between methadone and antidepressants (Antoniou et al.), use of antiseizure medications among pregnant women (Shouman et al.), and prescribing cascades related to anticholinergic medications (Trenaman et al.). Authors asked central and potentially clinically-influencing questions related to predicting medication adherence after a myocardial infarction (Campain et al.), repurposing of hydralazine to reduce phelbotomy (Lin et al.), comparison of time to treatment intensifications for diabetes treatments with newer drugs (Roberto et al.), and treatment failure with long-acting antipsychotics (Janzen et al.).

Papers also showcased the ability to assess policy-relevant questions such as the impact of policies on fentanyl prescribing (García-Sempere et al.), opioid use at the end-of-life (Minard et al.), biosimilar uptake of insulin glargine (Hayes et al.), trends in psoriatic arthritis medication use (Faria et al.), and the impact of COVID-19 on psychotropic medication use (Leong et al.). And lastly, this topic area showcased ongoing work related to novel data sources and use of data such as emerging use of Drug utilization research in barzil (Leal et al.), and use of pharmacy and registry data (Serhal et al.).

Conclusion

With the ubiquity of big data and limitations of RCTs, decision-makers and clinicians are in need of supportive evidence to support the assessment of drug effectiveness, safety, optimal use and policy decisions. This special topic showcased the global power of pharmacoepidemiology for answering this call.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 14 January 2022
doi: 10.3389/fphar.2021.812018

Comparative Effectiveness and Safety of Low-Dose Oral Anticoagulants in Patients With Atrial Fibrillation

Sylvie Perreault[1], Alice Dragomir[2], Robert Côté[3], Aurélie Lenglet[4,5], Simon de Denus[1,6], Marc Dorais[7], Brian White-Guay[8], James Brophy[9], Mireille E. Schnitzer[1], Marie-Pierre Dubé[6,8] and Jean-Claude Tardif[6,8]*

[1]Faculty of Pharmacy, Université de Montréal, Montreal, QC, Canada, [2]Department of Urology, Faculty of Medicine, University McGill, Montreal, QC, Canada, [3]Faculty of Medicine, Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada, [4]Laboratory MP3CV, Faculty of Pharmacy, University of Picardie Jules Verne, Amiens, France, [5]Pharmacy, Amiens University Medical Center, Amiens, France, [6]Montreal Heart Institute, Montreal, QC, Canada, [7]StatSciences Inc., Notre-Dame-de-l'Île-Perrot, QC, Canada, [8]Faculty of Medicine, Université de Montréal, Montreal, QC, Canada, [9]Faculty of Medicine, McGill University, Montreal, QC, Canada

OPEN ACCESS

Edited by:
Mina Tadrous, Women's College Hospital, Canada

Reviewed by:
Johannes P. Mouton, University of Cape Town, South Africa
Eva Kline-Rogers, University of Michigan, United States

***Correspondence:**
Sylvie Perreault
sylvie.perreault@umontreal.ca

Specialty section:
This article was submitted to Experimental Pharmacology and Drug Discovery, a section of the journal Frontiers in Pharmacology

Received: *09 November 2021*
Accepted: *28 December 2021*
Published: *14 January 2022*

Citation:
Perreault S, Dragomir A, Côté R, Lenglet A, de Denus S, Dorais M, White-Guay B, Brophy J, Schnitzer ME, Dubé M-P and Tardif J-C (2022) Comparative Effectiveness and Safety of Low-Dose Oral Anticoagulants in Patients With Atrial Fibrillation. Front. Pharmacol. 12:812018. doi: 10.3389/fphar.2021.812018

Aims: Observational studies of various dose levels of direct oral anticoagulants (DOACs) for patients with atrial fibrillation (AF) found that a high proportion of patients received a dose lower than the target dose tested in randomized controlled trials. There is a need to compare low-dose DOACs with warfarin or other DOACs on effectiveness and safety.

Methods: Using administrative data from Quebec province, Canada, we built a cohort of new warfarin or DOAC users discharged from hospital between 2011 and 2017. We determined CHA_2DS_2-VASc and HAS-BLED scores, and comorbidities for 3-year prior cohort entry. The primary effectiveness endpoint was a composite of ischemic stroke/systemic embolism (SE), and secondary outcomes included a safety composite of major bleeding (MB) events and effectiveness composite (stroke/SE, death) at 1-year follow-up. We contrasted each low-dose DOAC with warfarin or other DOACs as references using inverse probability of treatment weighting to estimate marginal Cox hazard ratios (HRs).

Results: The cohort comprised 22,969 patients (mean age: 80–86). We did not find a significant risk reduction for the stroke/SE primary effectiveness endpoint for DOACs vs. warfarin; however, we observed a significantly lower risk for low-dose dabigatran vs. warfarin (HR [95%CI]: 0.59 [0.42–0.81]) for effectiveness composite, mainly due to a lower death rate. The differences in effectiveness and safety composites between low-dose rivaroxaban vs. warfarin were not significant. However, low-dose apixaban had a better safety composite (HR: 0.68 [0.53–0.88]) vs. warfarin. Comparisons of dabigatran vs. apixaban showed a lower risk of stroke/SE (HR: 0.53 [0.30–0.93]) and a 2-fold higher risk of MB. The MB risk was higher for rivaroxaban than for apixaban (HR: 1.58 [1.09–2.29]).

Conclusions: The results of this population-based study suggest that low-dose dabigatran has a better effective composite than warfarin. Compared with apixaban, low-dose dabigatran had a better effectiveness composite but a worse safety profile. Low-dose apixaban had a better safety composite than warfarin and other low-dose DOACs.

Given that the comparative effectiveness and safety seem to vary from one DOAC to another, pharmacokinetic data for specific populations are now warranted.

Keywords: atrial fibrillation, oral anticoagulant, effectiveness outcomes, safety outcomes, low dose

INTRODUCTION

Atrial fibrillation (AF) is known to cause embolic stroke, and the prevalence of AF is likely to increase (Colilla et al., 2013). Ischemic strokes associated with AF are more severe and more lethal than strokes in the absence of AF (McGrath et al., 2013). Oral anticoagulant (OAC) therapy with direct oral anticoagulants (DOACs, such as dabigatran, rivaroxaban, apixaban, and edoxaban) or vitamin K antagonists (e.g., warfarin) can effectively prevent ischemic events (including strokes) in patients with non-valvular AF (Hart et al., 2007; Culebras and Messé, 2014; January et al., 2014; Lip et al., 2018). The optimal use of warfarin becomes more difficult in older adults, since the latter have a greater risk of both thromboembolic and bleeding events (Samsa and Matchar, 2000; Fanikos et al., 2005; Miyasaka et al., 2006). The difficulties associated with warfarin use have led to the widespread acceptance of fast-acting DOACs, which target specific clotting factors. DOACs are associated with a lower risk of drug interactions, are less influenced by dietary factors, and constitute alternatives to warfarin for the prevention of stroke and systemic embolism (SE) in patients with non-valvular AF (January et al., 2014; Lip et al., 2018).

The use of DOACs in patients with non-valvular AF has been studied in large randomized controlled trials (RCTs) (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Xu et al., 2016). Compared with warfarin, DOACs were shown to be superior or comparable in terms of efficacy and had similar or lower bleeding rates—especially for intracranial hemorrhage (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Xu et al., 2016). Recent real-world, population-based studies of DOAC use by patients with AF (Maura et al., 2017; Perreault et al., 2020) found that a low dose was more prevalent than the standard dose used in RCTs (Perreault et al., 2020).

Extrapolating the RCT data on DOAC doses to clinical decision-making is limited by the small number of patients included in RCTs (Connolly et al., 2009; Connolly et al., 2010; Granger et al., 2011; Patel et al., 2011). Variability in treatment adherence and patient follow-up constitutes an additional challenge in clinical management and is not optimally reflected by the RCT results (Steinberg et al., 2013; Cutler et al., 2014). Hence, there is a need to compare various low-dose DOACs with warfarin and each other in terms of effectiveness and safety in patients with AF. To address this gap in our knowledge, we built a cohort of hospitalized patients with a primary or secondary diagnosis of AF and then compared low-dose DOACs with warfarin and with each other.

MATERIALS AND METHODS

Data Source

We built a cohort using data in the Med-Echo administrative databases (hospital discharges), medical services, and public drug plans administered by the Régie de l'Assurance Maladie du Québec (RAMQ). The databases were linked using encrypted health insurance numbers. Information from these databases provides a complete picture of hospital admissions (Tamblyn et al., 1995; Tamblyn et al., 2000; Wilchesky et al., 2004; Eguale et al., 2010). The protocol was approved by an independent ethics committee at the University of Montreal.

Population-Based Cohort

The cohort was designed using claims data from the Quebec RAMQ and Med-Echo databases. We identified adult patients with a primary or secondary diagnosis of AF (inpatient codes: ICD-9 427.3, 427.31, or 427.32 or ICD-10 I48) discharged alive from hospital into the community between January 1st, 2011, and December 31st, 2017 (Humphries et al., 2004; Perreault et al., 2018). For patients with multiple admissions with an AF diagnosis, only the first admission was analyzed. In previous validation studies, the diagnostic performance of ICD-9 codes for AF was relatively good, with median positive predictive values of over 80% (Jensen et al., 2012).

We next identified patients who had filled a new prescription of apixaban (2.5 mg twice daily), dabigatran (110 mg twice daily), rivaroxaban (15 mg once daily) or warfarin in the 12 months following hospital discharge. These new users had not been exposed to any OACs in the year before the index claim date. Eligible patients also had to have continuous health insurance coverage for at least 12 months before the index claim date. The date of the first OAC claim after hospital discharge was taken as the date of cohort entry.

We excluded patients with end-stage chronic kidney disease or a kidney transplant, patients on dialysis at any time in the 3 years before the index date, those having undergone hip or knee replacement surgery in the 6 weeks before the index date, and those with a diagnosis of deep vein thrombosis or pulmonary embolism at baseline. We also excluded patients with a coagulation deficiency or having undergone certain medical procedures (including cardiac catheterization, stent placement, a coronary artery bypass graft, medical procedures for cerebrovascular disease, or defibrillator implantation) in the 3 months prior to the index date. Lastly, we excluded patients having undergone a cardiac valvular replacement in the 5 years prior to cohort entry.

Exposure to Oral Anticoagulants

We used fill dates and the number of days' supply per prescription to establish the dates of the patients' exposure to DOACs or warfarin. Patients were categorized as being on treatment if they had filled prescriptions within 30 days of the end of the previous treatment period. A gap of 30 days or less between treatments was allowed; this is a reasonable duration because of the DOACs' short half-life *in vivo* (Perreault et al., 2020). Consequently, we

chose 1 month as the allowable gap, which corresponds to an adherence of 92% or more over the fixed 12-month exposure assessment period.

Outcomes

The primary effectiveness outcome was a primary diagnosis of ischemic stroke or systemic embolism (SE) after hospital admission for acute care during the 12-month follow-up period. The secondary outcomes were 1) a safety composite of major bleeding events (intracranial hemorrhage (ICH), gastrointestinal hemorrhage, and all other bleeding events), 2) a benefit/risk composite (stroke/SE, major bleeding, and all-cause mortality), 3) all-cause mortality, 4) an effectiveness composite (stroke/SE and all-cause mortality), and 5) major bleeding (intracranial hemorrhage and gastrointestinal bleeding only) over the same period of follow-up.

We identified outcomes using ICD-9 or ICD-10 codes for the primary diagnosis of inpatient claims (**Supplementary Table S1**). The positive predictive values were over 80% (Levy et al., 1999; Blais et al., 2012). These codes performed relatively well in previous validation studies (Tirschwell and Longstreth, 2002; Blais et al., 2012; Jensen et al., 2012; Thigpen et al., 2015). The definition of major bleeding has been published previously (Perreault et al., 2018).

Demographic and Clinical Characteristics of the Study Population

We documented the demographic data at cohort entry. Social and economic deprivation was assessed using the Pampalon index (Pampalon et al., 2009). We determined the presence of comorbidities from specific ICD-9 or ICD-10 codes recorded during the hospital stay and those recorded for inpatient and outpatient diagnoses during the 3 years prior to the index date (Blais et al., 2012; Roy et al., 2020). Using the data on patient characteristics and associated comorbidities, we then assessed the CHA_2DS_2-VASc score (**Supplementary Tables S2, S3**), the modified HAS-BLED score (**Supplementary Tables S2, S4**) (Lip et al., 2010; Friberg et al., 2012; Pisters et al., 2010). and the Charlson Comorbidity Index(Deyo et al., 1992; D'Hoore et al., 1996). A frailty score (based on an appropriate risk assessment index for the elderly) was evaluated for the two years preceding cohort entry (Crane et al., 2010; Fillion et al., 2019). Lastly, we assessed the prescriptions filled for several medications in the 2 weeks preceding cohort entry. Although data on aspirin claims were recorded, possible over-the-counter purchases might have made this variable less reliable.

Statistical Analyses

We used descriptive statistics to summarize the patients' demographic and clinical characteristics as a function of the DOAC initially prescribed after discharge from hospital.

In order to balance the distribution of baseline patient characteristics between groups, an inverse probability of treatment weighting (IPTW) method was employed (Austin and Stuart, 2015; Allan et al., 2020). We created IPTW populations for the following contrasts: 1) low-dose dabigatran vs. warfarin; 2) low-dose rivaroxaban vs. warfarin; 3) low-dose apixaban vs. warfarin; 4) low-dose dabigatran vs. apixaban; 5) low-dose rivaroxaban vs. apixaban; 6) low-dose dabigatran vs. rivaroxaban. We used a multivariable logistic regression model to estimate the propensity score defined as the probability of being in the observed (actual) treatment group, conditional on all baseline covariates. The IPTW weights used the inverse of the propensity score. This weighting creates a pseudo-population in which there is balance across treatment groups with respect to covariates included in the model (**Supplementary Table S5**). The IPTW approach attempts to minimize the impact of confounding bias in observational studies by approximating a randomization process used in randomized clinical trials. All weights were stabilized by multiplying by the marginal probability of being in the treatment group.

Descriptive statistics were used to characterize the patients after weighting by IPTW. We estimated standardized differences in baseline characteristics between the treatment groups, where differences > 10% may suggest meaningful imbalance (Austin and Stuart, 2015). For descriptive analyses, we presented the pre- and post-weighted between-group comparisons. We reported the outcomes per 100 person-years for each treatment in each IPTW population.

Patients were followed from the index date until the earliest of the following events: outcome, being institutionalized or hospitalized for more than 15 days, discontinuation of treatment, or switching to another oral anticoagulant or to another dosage, end of study, or death, whichever came first. The censoring was handled by the Cox proportional hazards model. We contrasted each low-dose DOAC with both warfarin and each other low-dose as references using IPTW to estimate marginal Cox hazard ratios (HRs) for outcomes under treatment (UT). We constructed confidence intervals using the validated robust standard error.

Sensitivity Analyses

We performed several sensitivity analyses of the effectiveness and safety composite outcomes for low-dose DOACs, relative to warfarin or to each other (Fralick et al., 2020). Firstly, we performed an intent-to-treat (ITT) analysis in which we removed the censoring criteria of drug discontinuation or switching, so that all patients were followed up for 365 days unless they were censored for another reason. Secondly, we calculated an E-value as a guide to the potential impact of unmeasured confounding (VanderWeele and Ding, 2017). The E-value indicates how strongly an unmeasured confounder should be associated with use of each low-dose DOAC (relative to warfarin or another DOAC) to change the observed effects on effectiveness or safety to null, depending on the measured covariates. Lastly, we assessed the risk of diabetes complications (primary code of hospitalization (ICD-9: 250.1-250.9, 357.2, 366.41; ICD-10: E10-E14 excluding E10.9, E11.9, E12.9, E13.0, E14.9) and pneumonia (ICD9 code: 480-488 ICD10: J09-J18) as negative control outcomes. And, we assessed the impact of temporal trends accounted in the analysis by including the date of cohort entry in the IPTW matching. All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc. Cary, NC, United States).

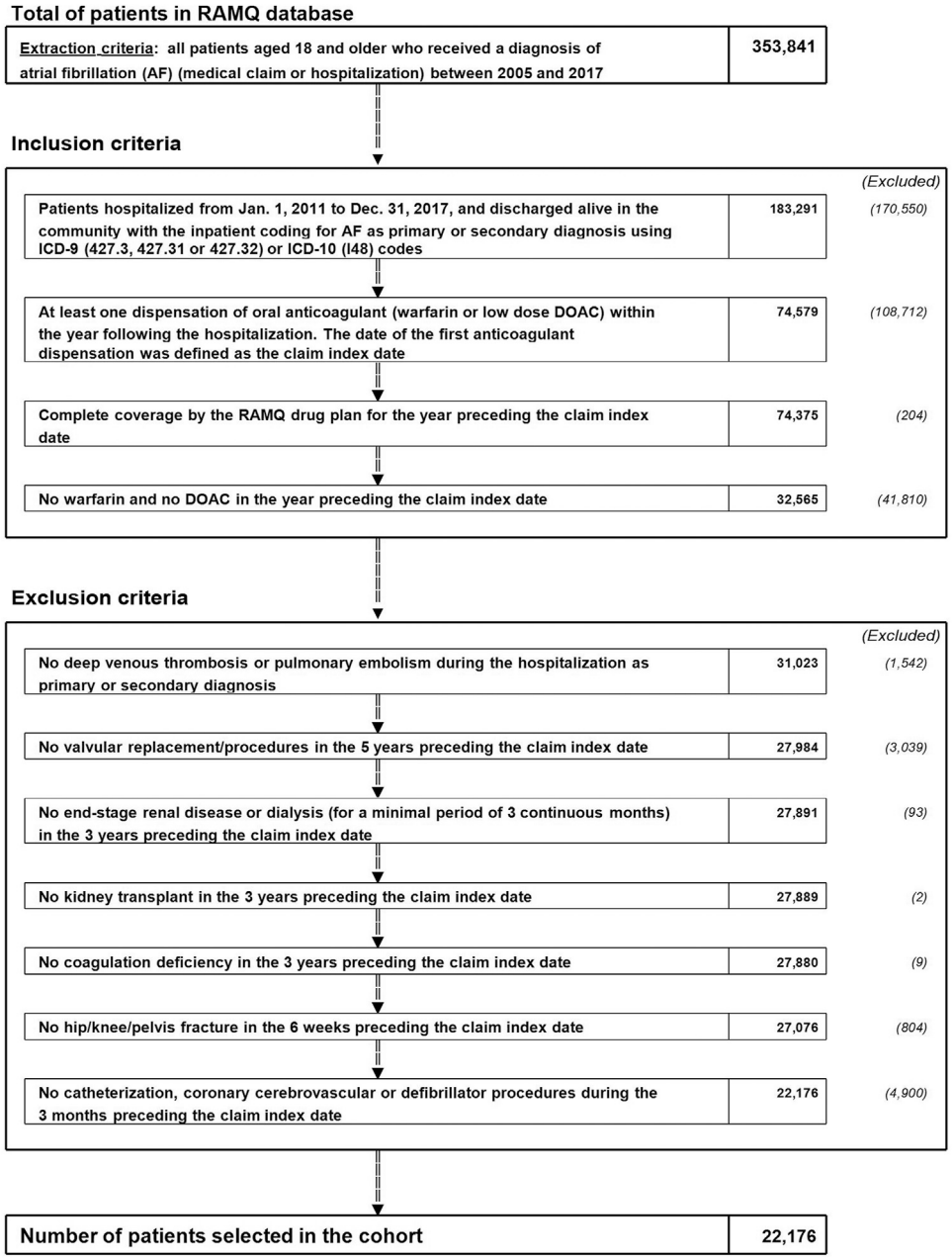


FIGURE 1 | Study flow chart. AF: atrial fibrillation; OAC: oral anticoagulant; RAMQ: Régie d'Assurance Maladie du Québec (Quebec administrative databases).

RESULTS

Demographics and Clinical Characteristics of the Study Population

A total of 22,176 patients with a confirmed diagnosis of AF received dabigatran (n = 1,929), rivaroxaban (n = 1,718), apixaban (n = 3,829) or warfarin (n = 14,700) (**Figure 1**). The characteristics of the study population for each DOAC after IPTW vs. warfarin are summarized in **Table 1**. In these groups, the mean age ranged from 80.2 to 82.2, and 55.8–58.9% were women. The characteristics of the study population for each DOAC after IPTW vs. the other DOACs are summarized in **Table 2**. In these groups, the mean age ranged from 82.0 to 85.3, and 59.6–66.1% were women. As shown in **Supplementary Tables S5.1–S5.6**, the absolute standardized differences in the IPTW populations were adequate.

Cumulative Incidence Rates

The annualized rates [95% confidence interval (CI)] for effectiveness and safety outcomes when comparing low-dose DOAC vs. warfarin in as-treated and intent-to-treat analyses after IPTW are shown in **Supplementary Tables S6.1, S6.2**.

TABLE 1 | Demographic and clinical characteristics of OAC users from 2011 to 2018, after IPTW (DOACs vs. warfarin).

	IPTW dabigatran and warfarin populations		IPTW rivaroxaban and warfarin populations		IPTW apixaban and warfarin populations	
	Dabigatran 110 mg twice daily (*N* = 1,929)	Warfarin (*n* = 14,700)	Rivaroxaban 15 mg once daily (*N* = 1,718)	Warfarin (*n* = 14,700)	Apixaban 2.5 mg twice daily (*n* = 3,829)	Warfarin (*n* = 14,700)
Age, years, mean ± SD	80.2 (7.7)	80.2 (9.1)	80.7 ± 7.8	80.4 ± 9.1	82.2 ± 7.9	81.5 ± 9.1
Females (%)	56.8%	55.8%	57.0%	56.1%	58.9%	58.2%
Pampalon index: elevated social deprivation	26.7%	26.6%	26.5%	26.6%	26.6%	26.6%
Pampalon index: elevated material deprivation	25.7%	25.9%	25.6%	25.9%	25.7%	25.9%
CHA_2DS_2-VASc score (mean ± SD)*	4.0 ± 1.3	3.9 ± 1.4	4.0 ± 1.3	4.0 ± 1.4	4.2 ± 1.3	4.0 ± 1.4
CHA_2DS_2-VASc score 0–1	2.6%	3.9%	2.6%	3.7%	1.5%	3.2%
CHA_2DS_2-VASc score 2–3	32.8%	31.9%	30.7%	31.5%	28.2%	29.8%
CHA_2DS_2-VASc score 4	32.5%	31.1%	33.5%	31.3%	33.2%	31.9%
CHA_2DS_2-VASc score ≥5	32.1%	33.1%	33.2%	33.5%	37.1%	35.1%
HAS-BLED score (mean ± SD)*	3.3 ± 1.2	3.0 ± 1.3	3.4 ± 1.3	3.3 ± 1.3	3.4 ± 1.3	3.3 ± 1.3
HAS-BLED score <3	25.7%	27.4%	25.9%	26.8%	23.9%	26.6%
HAS-BLED score ≥3	74.3%	72.6%	74.1%	73.2%	76.1%	73.4%
Charlson comorbidity index*						
Charlson comorbidity index (mean ± SD)	4.9 ± 3.5	4.9 ± 3.4	5.2 ± 3.7	5.0 ± 3.4	5.3 ± 3.5	5.0 ± 3.4
Charlson comorbidity index (median [IQR])	4.0 (2.0–7.0)	4.0 (2.0–7.0)	5.0 (3.0–7.0)	4.0 (2.0–7.0)	5.0 (3.0–7.0)	4.0 (2.0–7.0)
Charlson comorbidity index < 4	40.9%	39.1%	36.6%	38.3%	34.0%	38.2%
Charlson comorbidity index ≥ 4	59.1%	60.9%	63.4%	61.7%	66.0%	61.8%
Frailty score (mean ± SD)	12.7 ± 6.9	12.6 ± 7.0	12.9 ± 6.9	12.6 ± 7.0	13.3 ± 6.9	12.9 ± 7.1
Robust (frailty score ≤ -1)	0%	0%	0%	0%	0%	0%
Well (frailty score: 0–3)	6.7%	8.0%	6.9%	7.9%	5.5%	7.2%
Well/comorbidities (frailty score: 4–8)	24.2%	25.4%	23.7%	25.2%	24.6%	24.6%
Pre-frail (frailty score: 9–15)	35.2%	33.0%	35.6%	33.1%	33.6%	33.5%
Frail (frailty score: ≥16)	33.9%	33.6%	33.8%	33.8%	36.3%	34.7%
Hypertension	84.4%	84.6%	86.0%	84.8%	86.1%	84.7%
Coronary artery disease	59.3%	59.1%	60.3%	59.4%	59.8%	58.8%
Acute myocardial infarction	14.0%	15.0%	16.5%	15.6%	17.1%	15.9%
Chronic heart failure	41.2%	43.1%	44.5%	43.6%	46.1%	44.0%
Cardiomyopathy	5.6%	6.2%	6.2%	6.3%	5.7%	6.1%
Other cardiac rhythm disorders	20.3%	20.7%	20.2%	20.2%	19.7%	20.1%
Valvular heart disease	22.3%	22.3%	22.0%	22.6%	23.2%	22.8%
Stroke/Transient ischemic attack	21.5%	21.4%	20.7%	20.9%	22.1%	20.8%
Peripheral vascular (arterial) disease	23.3%	24.4%	25.6%	24.7%	25.9%	24.4%
Dyslipidemia	51.8%	53.4%	53.2%	53.5%	53.2%	52.7%
Diabetes	35.0%	37.9%	38.8%	38.0%	37.7%	36.8%
Major bleeding	31.8%	32.4%	34.8%	32.8%	36.1%	33.1%
Major intracranial bleeding	3.6%	3.4%	4.4%	3.4%	5.1%	3.4%
Major gastrointestinal bleeding	8.9%	8.1%	8.4%	8.2%	9.3%	8.1%
Major bleeding at other sites	24.3%	25.4%	27.2%	25.9%	27.4%	26.4%
Chronic renal failure	42.6%	43.3%	49.0%	45.1%	51.3%	45.9%

(Continued on following page)

TABLE 1 | (*Continued*) Demographic and clinical characteristics of OAC users from 2011 to 2018, after IPTW (DOACs vs. warfarin).

	IPTW dabigatran and warfarin populations		IPTW rivaroxaban and warfarin populations		IPTW apixaban and warfarin populations	
	Dabigatran 110 mg twice daily (*N* = 1,929)	**Warfarin (*n* = 14,700)**	**Rivaroxaban 15 mg once daily (*N* = 1,718)**	**Warfarin (*n* = 14,700)**	**Apixaban 2.5 mg twice daily (*n* = 3,829)**	**Warfarin (*n* = 14,700)**
Chronic renal failure ≤30 ml/min	5.7%	7.4%	7.2%	7.6%	8.6%	7.2%
Acute renal failure	25.1%	27.6%	30.9%	29.1%	33.6%	29.5%
Liver disease	2.2%	2.2%	2.6%	2.2%	2.4%	2.1%
Chronic obstructive pulmonary disease/asthma	37.6%	38.5%	40.5%	38.8%	37.6%	37.9%
Helicobacter pylori infection	0.8%	0.8%	1.5%	0.8%	0.6%	0.8%
Depression	11.8%	11.5%	11.0%	11.4%	11.3%	11.5%
Medical procedures*						
Cardiac catheterization	3.5%	3.8%	3.9%	3.8%	3.8%	3.7%
Percutaneous coronary intervention—stent	3.6%	2.9%	3.3%	3.0%	2.9%	2.8%
Coronary artery bypass grafting	1.0%	0.7%	0.9%	0.7%	0.5%	0.6%
Medical procedures for cerebrovascular disease	1.0%	1.1%	1.3%	1.1%	1.3%	1.0%
Medical procedures for a defibrillator	0.8%	0.5%	0.1%	0.4%	0.0%	0.4%
Medications (2 weeks prior cohort entry)						
Statin	46.8%	47.4%	47.5%	47.3%	46.0%	46.4%
Antiplatelet agents (excluding low-dose ASA)	6.2%	6.0%	6.3%	6.1%	6.2%	6.1%
Low-dose ASA	31.8%	31.5%	31.3%	31.4%	30.9%	30.8%
Proton pump inhibitors	46.1%	45.8%	46.2%	45.7%	47.0%	45.7%
NSAIDs	1.4%	1.4%	1.3%	1.3%	1.3%	1.3%
Digoxin	14.6%	13.5%	12.9%	13.3%	12.3%	12.8%
Amiodarone or propafenone	9.9%	10.1%	10.4%	10.1%	9.7%	10.1%
Antidepressants	9.0%	8.7%	8.5%	8.7%	8.5%	8.8%
B-blockers	60.8%	62.2%	62.2%	62.4%	61.2%	62.9%
Calcium channel blockers	39.1%	39.6%	39.7%	39.8%	40.8%	39.9%
Renin-angiotensin system inhibitors	38.9%	38.2%	38.3%	37.8%	37.3%	37.3%
Diuretics	42.3%	43.4%	45.6%	44.1%	46.1%	44.2%
Loop diuretics	35.2%	36.2%	38.6%	36.8%	39.2%	37.3%
Antidiabetics	20.8%	22.4%	23.4%	22.5%	21.9%	21.7%
PGP inhibitor use‡	61.0%	61.6%	61.9%	61.9%	62.1%	61.7%
Medical services (in the year prior to entry,%)						
Number of visits to a specialist (mean ± SD)	1.3 ± 2.2	1.2 ± 2.3	1.2 ± 2.0	1.2 ± 2.1	1.2 ± 2.2	1.2 ± 2.4
Number of family physician visits (mean ± SD)	1.3 ± 3.0	1.3 ± 3.0	1.3 ± 2.9	1.3 ± 3.0	1.3 ± 2.8	1.3 ± 3.0
Number of emergency room visits (mean ± SD)	3.3 ± 2.8	3.2 ± 2.8	3.3 ± 2.6	3.2 ± 2.8	3.3 ± 2.6	3.2 ± 2.8
Hospital services (in the 3 years prior to entry,%)						
≥2 all-cause hospital admissions	61.8%	58.3%	59.3%	58.2%	57.4%	58.0%
Number of all-cause hospital admissions (mean admission (±SD)	2.4 ± 1.7	2.4 ± 1.8	2.4 ± 2.0	2.4 ± 1.8	2.4 ± 1.9	2.4 ± 1.9
Hospital length of stay (mean ± SD)	11.1 ± 14.2	10.8 ± 12.0	11.1 ± 13.4	10.8 ± 12.0	11.2 ± 13.2	11.2 ± 13.2

**In the 3 years to the cohort entry; ‡P-glycoprotein. IPTW: inverse probability of treatment weighting; †Antidepressants: SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline)*

TABLE 2 | Demographic and clinical characteristics of OACs users from 2011 to 2018, after IPTW (comparisons of DOACs).

	IPTW dabigatran and apixaban populations		IPTW rivaroxaban and apixaban populations		IPTW dabigatran and rivaroxaban populations	
	Dabigatran 110 mg twice daily (*N* = 1,929)	Apixaban 2.5 mg twice daily (*n* = 3,829)	Rivaroxaban 15 mg once daily (*N* = 1,718)	Apixaban 2.5 mg twice daily (*n* = 3,829)	Dabigatran 110 mg twice daily (*N* = 1,929)	Rivaroxaban 15 mg once daily (*N* = 1,718)
Age—mean ± SD	84.2 ± 6.6	84.2 ± 7.8	85.3 ± 6.7	85.2 ± 7.0	81.9 ± 7.0	82.0 ± 7.5
Female (%)	64.5%	64.9%	65.8%	66.1%	59.6%	59.8%
Pampalon index elevated social deprivation	26.6%	26.6%	26.5%	26.6%	26.6%	26.5%
Pampalon index elevated material deprivation	25.7%	25.7%	25.6%	25.7%	25.7%	25.6%
CHA_2DS_2-VASc score (mean ± SD)*	4.1 ± 1.2	4.1 ± 1.3	4.2 ± 1.2	4.2 ± 1.2	3.9 ± 1.2	3.9 ± 1.3
CHA_2DS_2-VASc score 0–1	0.9%	1.4%	0.8%	0.9%	1.7%	2.7%
CHA_2DS_2-VASc score 2–3	28.5%	28.4%	25.8%	26.1%	34.5%	33.3%
CHA_2DS_2-VASc score 4	36.4%	35.1%	37.4%	36.1%	35.5%	34.8%
CHA_2DS_2-VASc score ≥5	34.2%	35.1%	36.0%	36.9%	28.3%	29.2%
HAS-BLED score (mean ± SD)*	3.2 ± 1.2	3.2 ± 1.3	3.2 ± 1.3	3.2 ± 1.3	3.0 ± 1.2	3.1 ± 1.3
HAS-BLED score <3	28.7%	31.1%	29.4%	28.9%	31.9%	34.0%
HAS-BLED score ≥3	71.3%	68.9%	70.6%	71.1%	68.1%	66.0%
Charlson score*						
Charlson comorbidity index (mean ± SD)	4.6 ± 3.4	4.6 ± 3.3	4.8 ± 3.4	4.7 ± 3.4	4.4 ± 3.4	4.4 ± 3.4
Charlson comorbidity index (median [IQR])	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (2.0–6.0)
Charlson comorbidity index <4	45.0%	43.2%	41.7%	41.2%	47.8%	48.0%
Charlson comorbidity index ≥4	55.0%	56.8%	58.3%	58.8%	52.2%	52.0%
Frailty score (mean ± SD)	13.1 ± 6.8	13.0 ± 7.0	13.3 ± 6.8	13.2 ± 6.9	12.2 ± 6.8	12.2 ± 6.7
Robust (frailty score ≤ −1)	0%	0%	0%	0%	0%	0%
Well (frailty score: 0–3)	6.3%	6.3%	5.3%	5.5%	8.0%	8.1%
Well/comorbidities (frailty score: 4–8)	23.1%	25.0%	22.8%	24.1%	26.1%	26.3%
Pre-frail (frailty score: 9–15)	35.0%	34.9%	37.9%	35.8%	35.2%	36.1%
Frail (frailty score: ≥16)	35.6%	33.8%	34.0%	34.6%	30.7%	29.5%
Hypertension	83.4%	83.1%	83.7%	83.9%	83.2%	82.9%
Coronary artery disease	52.4%	52.7%	53.2%	53.4%	52.5%	52.5%
Acute myocardial infarction	13.9%	14.4%	15.8%	15.8%	11.9%	12.2%
Chronic heart failure	40.2%	40.4%	42.1%	41.7%	36.7%	36.8%
Cardiomyopathy	4.5%	4.9%	5.0%	5.2%	5.0%	4.9%
Other cardiac rhythm disorders	20.1%	19.9%	18.3%	18.5%	20.7%	20.5%
Valvular heart disease	20.6%	20.5%	21.1%	21.2%	18.2%	18.2%
Stroke/Transient ischemic attack	21.6%	20.5%	19.6%	19.2%	20.7%	20.4%
Peripheral vascular (arterial) disease	20.3%	20.2%	21.0%	21.2%	20.2%	20.5%
Dyslipidemia	47.9%	49.2%	49.3%	49.6%	50.0%	49.7%
Diabetes	28.7%	29.4%	30.0%	29.7%	30.5%	29.9%
Major bleeding	33.5%	32.3%	33.1%	33.1%	29.3%	29.0%
Major intracranial bleeding	3.3%	5.0%	4.0%	4.6%	3.2%	3.7%
Major gastrointestinal bleeding	9.1%	7.9%	7.3%	8.2%	8.7%	7.1%
Major bleeding at other sites	26.0%	24.1%	26.4%	25.2%	21.9%	22.3%
Chronic renal failure	39.3%	38.3%	43.3%	43.5%	32.7%	32.8%

(Continued on following page)

TABLE 2 | (*Continued*) Demographic and clinical characteristics of OACs users from 2011 to 2018, after IPTW (comparisons of DOACs).

	IPTW dabigatran and apixaban populations		IPTW rivaroxaban and apixaban populations		IPTW dabigatran and rivaroxaban populations	
	Dabigatran 110 mg twice daily (*N* = 1,929)	**Apixaban 2.5 mg twice daily (*n* = 3,829)**	**Rivaroxaban 15 mg once daily (*N* = 1,718)**	**Apixaban 2.5 mg twice daily (*n* = 3,829)**	**Dabigatran 110 mg twice daily (*N* = 1,929)**	**Rivaroxaban 15 mg once daily (*N* = 1,718)**
Chronic renal failure ≤30 ml/min	3.4%	2.8%	3.7%	3.4%	2.1%	2.2%
Acute renal failure	23.5%	23.0%	27.0%	27.1%	18.6%	18.7%
Liver disease	1.8%	1.8%	1.5%	1.7%	2.0%	1.9%
Chronic obstructive pulmonary disease/asthma	35.1%	34.4%	35.0%	35.2%	36.3%	36.1%
Helicobacter pylori infection	0.8%	0.6%	1.2%	0.6%	0.7%	1.2%
Depression	12.6%	12.8%	12.3%	12.4%	13.1%	13.1%
Medical procedures*						
Cardiac catheterization	2.9%	2.7%	2.7%	2.6%	2.9%	2.8%
Percutaneous coronary intervention—stent	2.3%	2.3%	2.5%	2.4%	2.4%	2.6%
Coronary artery bypass grafting	0.3%	0.2%	0.3%	0.3%	0.6%	0.6%
Medical procedures for cerebrovascular disease	1.0%	0.7%	0.7%	0.7%	0.9%	0.9%
Medical procedures for a defibrillator	0.2%	0.0%	0.02%	0.00%	0.3%	0.3%
Medications (2 weeks prior to entry)						
Statin	41.0%	41.9%	40.8%	41.3%	42.8%	43.0%
Antiplatelets agents exclusing low-dose ASA)	6.0%	5.5%	5.7%	5.7%	5.1%	4.9%
Low-dose ASA	28.3%	26.9%	26.5%	26.4%	27.7%	27.4%
Proton pump inhibitors	43.7%	43.8%	43.7%	43.6%	43.1%	42.9%
NSAIDs	1.3%	1.3%	1.1%	1.1%	1.3%	1.3%
Digoxin	11.9%	11.6%	11.1%	10.9%	12.9%	12.9%
Amiodarone or propafenone	10.4%	9.7%	9.6%	9.8%	10.1%	9.9%
Antidepressants	10.5%	10.1%	9.6%	9.8%	9.5%	9.2%
B-blockers	63.3%	63.4%	65.1%	64.7%	62.9%	63.1%
Calcium channel blockers	39.6%	38.8%	38.9%	39.2%	37.8%	37.5%
Renin-angiotensin system inhibitors	38.4%	37.0%	35.3%	35.6%	39.2%	39.3%
Diuretics	41.0%	40.7%	42.0%	42.4%	38.8%	38.7%
Loop diuretics	34.4%	34.1%	35.1%	35.5%	30.8%	30.8%
Antidiabetics	16.7%	17.2%	17.2%	17.0%	17.7%	17.1%
PGP inhibitor use‡	59.4%	59.8%	60.5%	60.4%	59.5%	59.3%
Medical services*						
Number of visits to a specialist (mean ± SD)	1.4 ± 2.9	1.3 ± 2.8	1.3 ± 2.5	1.3 ± 2.6	1.3 ± 2.6	1.3 ± 2.5
Number of family physician visits (mean ± SD)	1.3 ± 3.0	1.3 ± 3.0	1.3 ± 2.9	1.3 ± 3.0	1.4 ± 3.1	1.4 ± 3.0
Number of emergency room visits (mean ± SD)	3.2 ± 2.6	3.3 ± 2.7	3.3 ± 2.4	3.3 ± 2.6	3.2 ± 2.8	3.2 ± 2.5
Hospital services (in the year before entry,%)						
≥2 all-cause hospital admissions	59.2%	54.8%	56.5%	54.1%	58.3%	57.4%
Number of all-cause hospital admissions (mean admission (±SD)	2.3 ± 1.5	2.3 ± 1.7	2.2 ± 1.6	2.2 ± 1.7	2.3 ± 1.6	2.3 ± 1.7
Hospital length of stay (mean ± SD)	10.1 ± 10.9	10.0 ± 11.3	10.3 ± 11.5	10.3 ± 11.5	9.4 ± 11.0	9.3 ± 10.9

**In the 3 years to the cohort entry; ‡P-glycoprotein. IPTW: inverse probability of treatment weighting; †Antidepressants: SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline)*

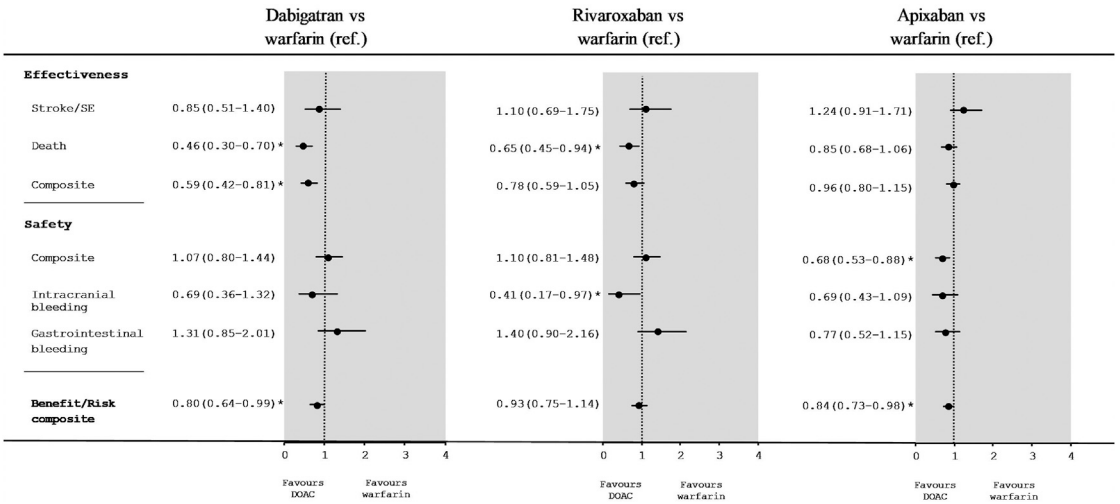


FIGURE 2 | Hazard ratios [95%CI] for low-dose DOACs vs. warfarin in an as-treated analysis of effectiveness and safety outcomes after IPTW.

Similarly, the rates for low-dose DOACs vs. the other DOACs are shown in **Supplementary Tables S6.3, S6.4**.

Effectiveness and Safety Outcomes of Direct Oral Anticoagulants vs. Warfarin

Figure 2 shows the HRs [95%CI] for the primary and secondary outcomes in IPTW populations taking low-dose DOACs vs. warfarin. The difference between dabigatran and warfarin was not statistically significant for the primary effectiveness outcome (stroke/SE) (HR [95%CI]: 0.85 [0.51–1.40]) and the safety composite (1.07 [0.80–1.44]). The HR [95%CI] for all-cause mortality was 0.45 (0.30–0.70]), the HR for the effectiveness composite was 0.59 [0.42–0.81] and the HR benefit/risk composite was 0.80 [0.64–0.99]). Similarly, the difference between rivaroxaban and warfarin was not statistically significant for the primary outcome (1.10 [0.69–1.75]), the safety composite (1.10 [0.81–1.48]) or the benefit/risk composite (0.93 [0.75–1.14]). The HR [95%CI] for all-cause mortality was 0.65 [0.45–0.94]). Lastly, there were no significant differences between apixaban and warfarin with regard to the primary outcome (HR [95%CI]: 1.24 [0.91–1.71]) but was significant for the safety composite (0.68 [0.53–0.88]) or the benefit/risk composite (0.84 [0.73–0.98]). The HR [95%CI] for all-cause mortality (0.85 [0.68–1.06]) was not statistically significant.

Effectiveness and Safety Outcomes When Comparing Direct Oral Anticoagulants With Each Other

Figure 3 shows the HRs [95%CI] for the effectiveness and safety outcomes in IPTW populations taking one low-dose DOAC vs. another low-dose DOAC. There was a significant difference between low-dose dabigatran and low-dose apixaban with regard to stroke/SE (HR [95%CI]: 0.53 [0.30–0.93]) and the safety composite (2.02 [1.42–2.86]) but not the benefit/risk composite (0.96 [0.75–1.22]). The HR was 0.43 ([0.26–0.71) for all-cause mortality and 0.49 ([0.34–0.71]) for the effectiveness composite. The HR for gastrointestinal bleeding was 2.47 ([1.47–4.16]).

There were no significant differences between of low-dose rivaroxaban and low-dose apixaban with regard to stroke/SE (HR: 0.70; [0.41–1.17]) or the benefit/risk composite (1.06 ([0.84–1.35]) but rivaroxaban presented a worse safety profile (1.58 (1.09–2.29]). When comparing low-dose dabigatran with low-dose rivaroxaban, we did not find significant differences for stroke/SE (HR: 0.80; [0.40–1.59]), the safety composite (HR: 1.16; [0.79–1.72]), or the benefit/risk composite (HR: 0.96; [0.72–1.28]).

Sensitivity Analyses

The Intent-To-Treat Analysis

Intention-to-treat (ITT) analyses of the IPTW populations followed up for 365 days gave consistent results (**Supplementary Tables S7.1, S7.2**) for all comparisons vs. warfarin or other DOACs.

The Impact of Unmeasured Confounders

For dabigatran vs. warfarin, the E-value corresponding to the CI boundary closest to 1 for the risk of death was 2.21 (**Table 3**). The observed HR for death might have been due to an unmeasured confounder that occurred 2.21 times more often in the dabigatran group than in the warfarin group and thus increased the death rate by a factor of 2. This assumes no correlation between the unmeasured confounder and the measured confounders used in the propensity score.

The E-value corresponding to the CI boundary closest to 1 for the various comparisons ranged from 1.36 to 3.62. Lastly, the E-value corresponding to the HR point estimates for the various comparisons ranged from 2.28 to 3.77—indicating that these situations are less likely to occur.

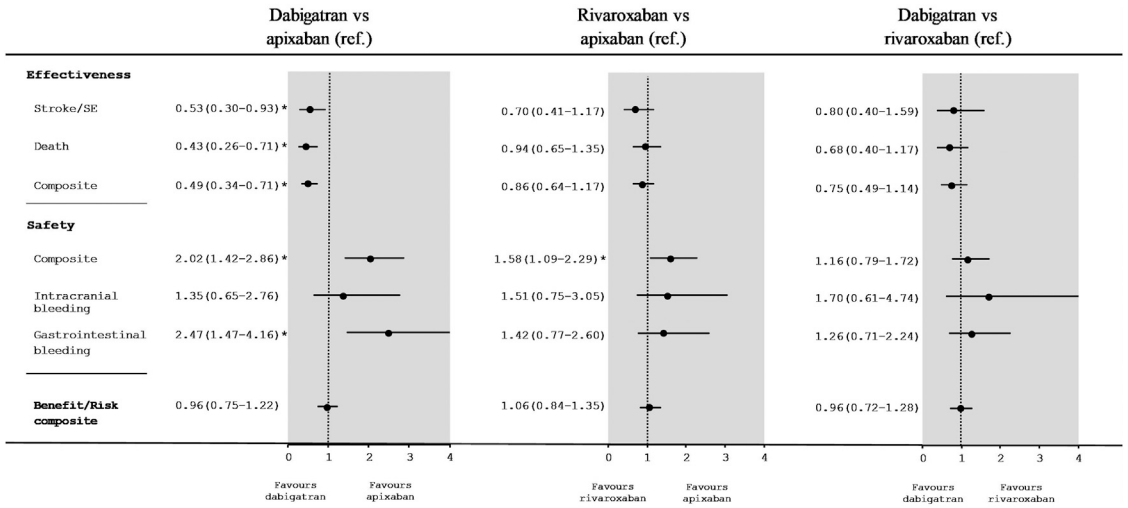


FIGURE 3 | Hazard ratios [95%CI] for comparisons between low-dose DOACs in an as-treated analysis of effectiveness and safety outcomes after IPTW.

TABLE 3 | E-values for significant comparisons (as-treated analysis) of low-dose DOACs with warfarin and with each other.

	Hazard ratio (95%CI)	E-value corresponding to the CI boundary closest to 1	E-value corresponding to the HR point estimate*
Low-dose dabigatran vs. warfarin			
Death	0.46* (0.30–0.70)	2.21	3.77
Effectiveness composite	0.55* (0.42–0.81)	1.77	3.04
Low-dose rivaroxaban vs. warfarin			
Death	0.65* (0.45–0.94)	2.45	2.45
Low-dose apixaban vs. warfarin			
Safety composite	0.68* (0.53–0.88)	1.53	2.30
Low-dose dabigatran vs. low-dose apixaban			
Stroke/systemic embolism	0.53* (0.30–0.93)	1.36	3.18
Death	0.43* (0.26–0.71)	2.17	4.08
Effectiveness composite	0.49* (0.34–0.71)	2.17	3.50
Gastrointestinal bleeding	2.47* (1.47–4.16)	2.30	4.38
Extracranial bleeding	2.30* (1.54–3.44)	2.45	4.03
Safety composite	2.02* (1.42–2.86)	2.19	3.46
Low-dose rivaroxaban vs. low-dose apixaban			
Extracranial bleeding	1.61* (1.04–2.49)	1.24	2.60
Safety composite	1.58* (1.09–2.29)	1.40	2.54

The Negative Control and Impact of the Temporal Trends

With regard to the rate per 100 person-years of pneumonia vs. warfarin and DOAC (**Supplementary Table S8**), none of the comparisons gave a significant HR. Moreover, the rates per 100 person-years of hospitalization for diabetes complications were quite similar for warfarin and DOACs, with no significant HRs. As expected, the results were similar in all the groups.

Similar results were observed for the overall comparative effectiveness and safety of each low-dose of DOACs versus warfarin (**Supplementary Table S7.3**) and also each low-dose of DOACs versus each other (**Supplementary Table S7.4**) with the inclusion of the base date of cohort entry in the IPTW matching. Some outcomes were marginally modified for the comparison versus warfarin mainly for rivaroxaban safety composite.

DISCUSSION

Low-Dose Direct Oral Anticoagulants Compared With Warfarin

In our population-based study, we did not observe a significant reduction in the risk of the primary outcome (stroke/SE) for any of the low-dose DOACs (dabigatran, rivaroxaban, and apixaban) vs. warfarin. Moreover, there were no significant relationships with the safety profile, except for low-dose apixaban vs. warfarin (a 32% risk reduction for apixaban). With regard to the secondary outcomes, low-dose dabigatran and low-dose rivaroxaban were associated with a reduction (vs. warfarin) in the risk of all-cause mortality that ranged from 35 to 54%.

Our effectiveness and safety results for patients using low-dose dabigatran or warfarin are quite similar to those published for the RE-LY study (Connolly et al., 2009). Although a number of observational studies have compared dabigatran, rivaroxaban, and apixaban with warfarin in terms of effectiveness and safety, (Graham et al., 2016; Larsen et al., 2016; Hernandez et al., 2017; Nielsen et al., 2017; Li et al., 2018; Lopes et al., 2018; Graham et al., 2019) but few reported on the impact of low dose levels. However, Li et al. evaluated the effectiveness and safety of different dose levels of apixaban (vs. warfarin) with a similar study design and in a similar patient population. Apixaban 2.5 mg twice daily was associated with a lower risk of major bleeding (HR [95%CI]: 0.59 [0.49–0.71]) (Li et al., 2018). Our results are also consistent with those of another similar study in which (relative to warfarin) low-dose apixaban and low-dose dabigatran had no significant effects on a stroke/SE outcome, low-dose dabigatran was associated with a reduction in the risk of death, and low-dose apixaban presented a better safety profile for bleeding events (Rahme et al., 2021).

Low-Dose Direct Oral Anticoagulants Compared With Each Other

Low-dose dabigatran presented a 47% difference in stroke/SE when compared with apixaban; however, it also had a less favorable safety profile, with more than a two-fold relative increase in the major bleeding risk. For low-dose rivaroxaban vs apixaban, we did not observe a significant difference in stroke/SE, although low-dose rivaroxaban had a less favorable safety composite. We noted no significant difference in the comparison of dabigatran and rivaroxaban for the effectiveness and safety outcomes.

The published RCTs did not perform head-to-head comparisons of different dose levels of DOACs. Furthermore, the observational studies of effectiveness and safety compared full dose levels of dabigatran, rivaroxaban, and apixaban—the three most widely used DOACs (Graham et al., 2019; Bonde et al., 2020; Fralick et al., 2020) A recent meta-analysis reported indirect comparisons, although the data on low-dose DOACs were scarce (Li et al., 2019). There were no significant differences in the stroke/SE outcome for rivaroxaban or dabigatran, when compared with apixaban. However, the risk of major bleeding was significantly higher for rivaroxaban than for apixaban (HR [95%CI]: 1.71 [1.51–1.94]). Moreover, a recent study reported nonsignificant differences in the stroke/SE outcome between low doses of dabigatran, rivaroxaban, and apixaban; however, apixaban had a better safety profile (Durand et al., 2021).

A recent placebo-controlled RCT in older Japanese patients with non-valvular AF (where a standard dose is not appropriate) found that edoxaban was efficacious in preventing stroke/SE and did not have any impact on major bleeding (other than gastrointestinal bleeding) (Okumura et al., 2020). In view of the lack of RCT data and the high prevalence of low-dose DOAC use, further studies of the effectiveness and safety of low-dose DOACs are clearly warranted. Moreover, given that the net benefit seems to vary from one DOAC to another, pharmacokinetic data for specific populations (such as those with higher risks of thrombosis and bleeding) must be generated by comparing plasma drug levels and factor Xa inhibition as a function of the dose level and the outcomes (Testa et al., 2018; Sukumar et al., 2019).

Our study had a number of strengths, including the large sample size and the analyses of the relative effectiveness and safety of low-dosage DOACs vs. warfarin and other DOACs in patients with AF. We assessed several clinical outcomes, in order to balance the overall benefits and risks. We used an IPTW population score model to build cohorts that were well balanced at baseline with regard to relevant factors, and we also performed several sensitivity analyses.

Our study also had some limitations. Firstly, this observational study was based on administrative data and so might have been subject to confounding bias by unadjusted factors (blood pressure control, laboratory values, international normalized ratio control, body weight, and estimated glomerular filtration rate) or to residual channeling bias. Secondly, most of our patients were older and ethnically white, and so our present results might not be generalizable to other patient settings (e.g., non-hospitalized individuals with AF), other age groups, or other ethnic groups (Shen et al., 2007). Lastly, residual bias is still possible—especially with regard to unmeasured variables and the healthy population effect.

The results of this population-based study suggest that low-dose dabigatran has a better effective composite than warfarin. Compared with apixaban, low-dose dabigatran had a better effectiveness composite but a worse safety profile. Low-dose apixaban had a better safety composite than warfarin and other low-dose DOACs. Studies of plasma drug levels and factor Xa inhibition as a function of the dose level and outcomes are now warranted, since the net benefit appears to vary from one DOAC to another.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee at the University of Montreal. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

The study was funded by the Heart and Stroke Foundation of Canada (G-17-0018326) and the Réseau Québécois de Recherche sur le Médicament (RQRM).

ACKNOWLEDGMENTS

We thank the RAMQ and Quebec Health Ministry for assistance with data handling and the Commission d'accès à l'information for authorizing the study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.812018/full#supplementary-material

REFERENCES

Allan, V., Ramagopalan, S. V., Mardekian, J., Jenkins, A., Li, X., Pan, X., et al. (2020). Propensity Score Matching and Inverse Probability of Treatment Weighting to Address Confounding by Indication in Comparative Effectiveness Research of Oral Anticoagulants. *J. Comp. Eff. Res.* 9 (9), 603–614. doi:10.2217/cer-2020-0013

Austin, P. C., and Stuart, E. A. (2015). Moving towards Best Practice when Using Inverse Probability of Treatment Weighting (IPTW) Using the Propensity Score to Estimate Causal Treatment Effects in Observational Studies. *Stat. Med.* 34 (28), 3661–3679. doi:10.1002/sim.6607

Blais, C. L. L., Hamel, D., Brown, K., Rinfret, S., Cartier, R., Giguère, M., et al. (2012). *Évaluation des soins et surveillance des maladies cardiovasculaires de santé publique du Québec et de L'institut national d'excellence en santé et services sociaux*, Gouvernement du Québec, Institut national de santé publique, Institut national d'excellence en santé et des services sociaux 1–9.

Bonde, A. N., Martinussen, T., Lee, C. J., Lip, G. Y. H., Staerk, L., Bang, C. N., et al. (2020). Rivaroxaban versus Apixaban for Stroke Prevention in Atrial Fibrillation: An Instrumental Variable Analysis of a Nationwide Cohort. *Circ. Cardiovasc. Qual. Outcomes* 13 (4), e006058. doi:10.1161/CIRCOUTCOMES.119.006058

Colilla, S., Crow, A., Petkun, W., Singer, D. E., Simon, T., and Liu, X. (2013). Estimates of Current and Future Incidence and Prevalence of Atrial Fibrillation in the U.S. Adult Population. *Am. J. Cardiol.* 112 (8), 1142–1147. doi:10.1016/j.amjcard.2013.05.063

Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., et al. (2009). Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N. Engl. J. Med.* 361 (12), 1139–1151. doi:10.1056/NEJMoa0905561

Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Reilly, P. A., and Wallentin, L. (2010). Newly Identified Events in the RE-LY Trial. *N. Engl. J. Med.* 363 (19), 1875–1876. doi:10.1056/NEJMc1007378

Crane, S. J., Tung, E. E., Hanson, G. J., Cha, S., Chaudhry, R., and Takahashi, P. Y. (2010). Use of an Electronic Administrative Database to Identify Older Community Dwelling Adults at High-Risk for Hospitalization or Emergency Department Visits: the Elders Risk Assessment index. *BMC Health Serv. Res.* 10, 338. doi:10.1186/1472-6963-10-338

Culebras, A., and Messé, S. R. (2014). Summary of Evidence-Based Guideline Update: Prevention of Stroke in Nonvalvular Atrial Fibrillation: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 83 (13), 1220. doi:10.1212/WNL.0000000000000831

Cutler, T. W., Chuang, A., Huynh, T. D., Witt, R. G., Branch, J., Pon, T., et al. (2014). A Retrospective Descriptive Analysis of Patient Adherence to Dabigatran at a Large Academic Medical center. *J. Manag. Care Spec. Pharm.* 20 (10), 1028–1034. doi:10.18553/jmcp.2014.20.10.1028

D'Hoore, W., Bouckaert, A., and Tilquin, C. (1996). Practical Considerations on the Use of the Charlson Comorbidity index with Administrative Data Bases. *J. Clin. Epidemiol.* 49 (12), 1429–1433. doi:10.1016/s0895-4356(96)00271-5

Deyo, R. A., Cherkin, D. C., and Ciol, M. A. (1992). Adapting a Clinical Comorbidity index for Use with ICD-9-CM Administrative Databases. *J. Clin. Epidemiol.* 45 (6), 613–619. doi:10.1016/0895-4356(92)90133-8

Durand, M., Schnitzer, M. E., Pang, M., Carney, G., Eltonsy, S., Filion, K. B., et al. (2021). Effectiveness and Safety Among Direct Oral Anticoagulants in Nonvalvular Atrial Fibrillation: A Multi-Database Cohort Study with Meta-Analysis. *Br. J. Clin. Pharmacol.* 87 (6), 2589–2601. doi:10.1111/bcp.14669

Eguale, T., Winslade, N., Hanley, J. A., Buckeridge, D. L., and Tamblyn, R. (2010). Enhancing Pharmacosurveillance with Systematic Collection of Treatment Indication in Electronic Prescribing: a Validation Study in Canada. *Drug Saf.* 33 (7), 559–567. doi:10.2165/11534580-000000000-00000

Fanikos, J., Grasso-Correnti, N., Shah, R., Kucher, N., and Goldhaber, S. Z. (2005). Major Bleeding Complications in a Specialized Anticoagulation Service. *Am. J. Cardiol.* 96 (4), 595–598. doi:10.1016/j.amjcard.2005.03.104

Fillion, V., Sirois, M. J., Gamache, P., Guertin, J. R., Morin, S. N., and Jean, S. (2019). Frailty and Health Services Use Among Quebec Seniors with Non-hip Fractures: a Population-Based Study Using Adminsitrative Databases. *BMC Health Serv. Res.* 19 (1), 70. doi:10.1186/s12913-019-3865-z

Fralick, M., Colacci, M., Schneeweiss, S., Huybrechts, K. F., Lin, K. J., and Gagne, J. J. (2020). Effectiveness and Safety of Apixaban Compared with Rivaroxaban for Patients with Atrial Fibrillation in Routine Practice: A Cohort Study. *Ann. Intern. Med.* 172 (7), 463–473. doi:10.7326/M19-2522

Friberg, L., Rosenqvist, M., and Lip, G. Y. (2012). Evaluation of Risk Stratification Schemes for Ischaemic Stroke and Bleeding in 182 678 Patients with Atrial Fibrillation: the Swedish Atrial Fibrillation Cohort Study. *Eur. Heart J.* 33 (12), 1500–1510. doi:10.1093/eurheartj/ehr488

Graham, D. J., Baro, E., Zhang, R., Liao, J., Wernecke, M., Reichman, M. E., et al. (2019). Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation. *Am. J. Med.* 132 (5), 596–e11. doi:10.1016/j.amjmed.2018.12.023

Graham, D. J., Reichman, M. E., Wernecke, M., Hsueh, Y. H., Izem, R., Southworth, M. R., et al. (2016). Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated with Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation. *JAMA Intern. Med.* 176 (11), 1662–1671. doi:10.1001/jamainternmed.2016.5954

Granger, C. B., Alexander, J. H., McMurray, J. J., Lopes, R. D., Hylek, E. M., Hanna, M., et al. (2011). Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N. Engl. J. Med.* 365 (11), 981–992. doi:10.1056/NEJMoa1107039

Hart, R. G., Pearce, L. A., and Aguilar, M. I. (2007). Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. *Ann. Intern. Med.* 146 (12), 857–867. doi:10.7326/0003-4819-146-12-200706190-00007

Hernandez, I., Zhang, Y., and Saba, S. (2017). Comparison of the Effectiveness and Safety of Apixaban, Dabigatran, Rivaroxaban, and Warfarin in Newly Diagnosed Atrial Fibrillation. *Am. J. Cardiol.* 120 (10), 1813–1819. doi:10.1016/j.amjcard.2017.07.092

Humphries, K. H., Jackevicius, C., Gong, Y., Svensen, L., Cox, J., Tu, J. V., et al. (2004). Population Rates of Hospitalization for Atrial Fibrillation/flutter in Canada. *Can. J. Cardiol.* 20 (9), 869–876.

January, C. T., Wann, L. S., Alpert, J. S., Calkins, H., Cigarroa, J. E., Cleveland, J. C., et al. (2014). 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the

Heart Rhythm Society. *J. Am. Coll. Cardiol.* 64 (21), e1–76. doi:10.1016/j.jacc.2014.03.022

Jensen, P. N., Johnson, K., Floyd, J., Heckbert, S. R., Carnahan, R., and Dublin, S. (2012). A Systematic Review of Validated Methods for Identifying Atrial Fibrillation Using Administrative Data. *Pharmacoepidemiol. Drug Saf.* 21 (Suppl. 1), 141–147. doi:10.1002/pds.2317

Larsen, T. B., Skjøth, F., Nielsen, P. B., Kjældgaard, J. N., and Lip, G. Y. (2016). Comparative Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants and Warfarin in Patients with Atrial Fibrillation: Propensity Weighted Nationwide Cohort Study. *BMJ* 353, i3189. doi:10.1136/bmj.i3189

Levy, A. R., Tamblyn, R. M., Fitchett, D., McLeod, P. J., and Hanley, J. A. (1999). Coding Accuracy of Hospital Discharge Data for Elderly Survivors of Myocardial Infarction. *Can. J. Cardiol.* 15 (11), 1277–1282.

Li, G., Lip, G. Y. H., Holbrook, A., Chang, Y., Larsen, T. B., Sun, X., et al. (2019). Direct Comparative Effectiveness and Safety between Non-vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Nonvalvular Atrial Fibrillation: a Systematic Review and Meta-Analysis of Observational Studies. *Eur. J. Epidemiol.* 34 (2), 173–190. doi:10.1007/s10654-018-0415-7

Li, X., Keshishian, A., Hamilton, M., Horblyuk, R., Gupta, K., Luo, X., et al. (2018). Apixaban 5 and 2.5 Mg Twice-Daily versus Warfarin for Stroke Prevention in Nonvalvular Atrial Fibrillation Patients: Comparative Effectiveness and Safety Evaluated Using a Propensity-Score-Matched Approach. *PLoS One* 13 (1), e0191722. doi:10.1371/journal.pone.0191722

Lip, G. Y., Nieuwlaat, R., Pisters, R., Lane, D. A., and Crijns, H. J. (2010). Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach: the Euro Heart Survey on Atrial Fibrillation. *Chest* 137 (2), 263–272. doi:10.1378/chest.09-1584

Lip, G. Y. H., Banerjee, A., Boriani, G., Chiang, C. E., Fargo, R., Freedman, B., et al. (2018). Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest* 154 (5), 1121–1201. doi:10.1016/j.chest.2018.07.040

Lopes, R. D., Steffel, J., Di Fusco, M., Keshishian, A., Luo, X., Li, X., et al. (2018). Effectiveness and Safety of Anticoagulants in Adults with Non-valvular Atrial Fibrillation and Concomitant Coronary/Peripheral Artery Disease. *Am. J. Med.* 131 (9), 1075–e4. doi:10.1016/j.amjmed.2018.05.007

Maura, G., Pariente, A., Alla, F., and Billionnet, C. (2017). Adherence with Direct Oral Anticoagulants in Nonvalvular Atrial Fibrillation New Users and Associated Factors: a French Nationwide Cohort Study. *Pharmacoepidemiol. Drug Saf.* 26 (11), 1367–1377. doi:10.1002/pds.4268

McGrath, E. R., Kapral, M. K., Fang, J., Eikelboom, J. W., Conghaile, Aó., O'Conghaile, A., et al. (2013). Association of Atrial Fibrillation with Mortality and Disability after Ischemic Stroke. *Neurology* 81 (9), 825–832. doi:10.1212/WNL.0b013e3182a2cc15

Miyasaka, Y., Barnes, M. E., Gersh, B. J., Cha, S. S., Bailey, K. R., Abhayaratna, W. P., et al. (2006). Secular Trends in Incidence of Atrial Fibrillation in Olmsted County, Minnesota, 1980 to 2000, and Implications on the Projections for Future Prevalence. *Circulation* 114 (2), 119–125. doi:10.1161/CIRCULATIONAHA.105.595140

Nielsen, P. B., Skjøth, F., Søgaard, M., Kjældgaard, J. N., Lip, G. Y., and Larsen, T. B. (2017). Effectiveness and Safety of Reduced Dose Non-vitamin K Antagonist Oral Anticoagulants and Warfarin in Patients with Atrial Fibrillation: Propensity Weighted Nationwide Cohort Study. *BMJ* 356, j510. doi:10.1136/bmj.j510

Okumura, K., Akao, M., Yoshida, T., Kawata, M., Okazaki, O., Akashi, S., et al. (2020). Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation. *N. Engl. J. Med.* 383 (18), 1735–1745. doi:10.1056/NEJMoa2012883

Pampalon, R., Hamel, D., Gamache, P., and Raymond, G. (2009). A Deprivation index for Health Planning in Canada. *Chronic Dis. Can.* 29 (4), 178–191. doi:10.24095/hpcdp.29.4.05

Patel, M. R., Mahaffey, K. W., Garg, J., Pan, G., Singer, D. E., Hacke, W., et al. (2011). Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N. Engl. J. Med.* 365 (10), 883–891. doi:10.1056/NEJMoa1009638

Perreault, S., de Denus, S., White-Guay, B., Côté, R., Schnitzer, M. E., Dubé, M. P., et al. (2020). Oral Anticoagulant Prescription Trends, Profile Use, and Determinants of Adherence in Patients with Atrial Fibrillation. *Pharmacotherapy* 40 (1), 40–54. doi:10.1002/phar.2350

Perreault, S., Shahabi, P., Cote, R., Dumas, S., Rouleau-Mailloux, É., Feroz Zada, Y., et al. (2018). Rationale, Design, and Preliminary Results of the Quebec Warfarin Cohort Study. *Clin. Cardiol.* 41 (5), 576–585. doi:10.1002/clc.22948

Pisters, R., Lane, D. A., Nieuwlaat, R., de Vos, C. B., Crijns, H. J., and Lip, G. Y. (2010). A Novel User-Friendly Score (HAS-BLED) to Assess 1-year Risk of Major Bleeding in Patients with Atrial Fibrillation: the Euro Heart Survey. *Chest* 138 (5), 1093–1100. doi:10.1378/chest.10-0134

Rahme, E., Godin, R., Nedjar, H., Dasgupta, K., and Tagalakis, V. (2021). Dose Specific Effectiveness and Safety of DOACs in Patients with Non-valvular Atrial Fibrillation: A Canadian Retrospective Cohort Study. *Thromb. Res.* 203, 121–130. doi:10.1016/j.thromres.2021.05.005

Roy, L., Zappitelli, M., White-Guay, B., Lafrance, J. P., Dorais, M., and Perreault, S. (2020). Agreement between Administrative Database and Medical Chart Review for the Prediction of Chronic Kidney Disease G Category. *Can. J. Kidney Health Dis.* 7, 2054358120959908. doi:10.1177/2054358120959908

Samsa, G. P., and Matchar, D. B. (2000). Relationship between Test Frequency and Outcomes of Anticoagulation: a Literature Review and Commentary with Implications for the Design of Randomized Trials of Patient Self-Management. *J. Thromb. Thrombolysis* 9 (3), 283–292. doi:10.1023/a:1018778914477

Shen, A. Y., Yao, J. F., Brar, S. S., Jorgensen, M. B., and Chen, W. (2007). Racial/ethnic Differences in the Risk of Intracranial Hemorrhage Among Patients with Atrial Fibrillation. *J. Am. Coll. Cardiol.* 50 (4), 309–315. doi:10.1016/j.jacc.2007.01.098

Steinberg, B. A., Holmes, D. N., Piccini, J. P., Ansell, J., Chang, P., Fonarow, G. C., et al. (2013). Early Adoption of Dabigatran and its Dosing in US Patients with Atrial Fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation. *J. Am. Heart Assoc.* 2 (6), e000535. doi:10.1161/JAHA.113.000535

Sukumar, S., Gulilat, M., Linton, B., Gryn, S. E., Dresser, G. K., Alfonsi, J. E., et al. (2019). Apixaban Concentrations with Lower Than Recommended Dosing in Older Adults with Atrial Fibrillation. *J. Am. Geriatr. Soc.* 67 (9), 1902–1906. doi:10.1111/jgs.15982

Tamblyn, R., Lavoie, G., Petrella, L., and Monette, J. (1995). The Use of Prescription Claims Databases in Pharmacoepidemiological Research: the Accuracy and Comprehensiveness of the Prescription Claims Database in Québec. *J. Clin. Epidemiol.* 48 (8), 999–1009. doi:10.1016/0895-4356(94)00234-h

Tamblyn, R., Reid, T., Mayo, N., McLeod, P., and Churchill-Smith, M. (2000). Using Medical Services Claims to Assess Injuries in the Elderly: Sensitivity of Diagnostic and Procedure Codes for Injury Ascertainment. *J. Clin. Epidemiol.* 53 (2), 183–194. doi:10.1016/s0895-4356(99)00136-5

Testa, S., Paoletti, O., Legnani, C., Dellanoce, C., Antonucci, E., Cosmi, B., et al. (2018). Low Drug Levels and Thrombotic Complications in High-Risk Atrial Fibrillation Patients Treated with Direct Oral Anticoagulants. *J. Thromb. Haemost.* 16 (5), 842–848. doi:10.1111/jth.14001

Thigpen, J. L., Dillon, C., Forster, K. B., Henault, L., Quinn, E. K., Tripodis, Y., et al. (2015). Validity of International Classification of Disease Codes to Identify Ischemic Stroke and Intracranial Hemorrhage Among Individuals with Associated Diagnosis of Atrial Fibrillation. *Circ. Cardiovasc. Qual. Outcomes* 8 (1), 8–14. doi:10.1161/CIRCOUTCOMES.113.000371

Tirschwell, D. L., and Longstreth, W. T., Jr. (2002). Validating Administrative Data in Stroke Research. *Stroke* 33 (10), 2465–2470. doi:10.1161/01.str.0000032240.28636.bd

VanderWeele, T. J., and Ding, P. (2017). Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann. Intern. Med.* 167 (4), 268–274. doi:10.7326/M16-2607

Wilchesky, M., Tamblyn, R. M., and Huang, A. (2004). Validation of Diagnostic Codes within Medical Services Claims. *J. Clin. Epidemiol.* 57 (2), 131–141. doi:10.1016/S0895-4356(03)00246-4

Xu, H., Ruff, C. T., Giugliano, R. P., Murphy, S. A., Nordio, F., Patel, I., et al. (2016). Concomitant Use of Single Antiplatelet Therapy with Edoxaban or Warfarin in

Patients with Atrial Fibrillation: Analysis from the ENGAGE AF-TIMI48 Trial. *J. Am. Heart Assoc.* 5 (2), e002587. doi:10.1161/JAHA.115.002587

Conflict of Interest: Author MD was employed by StatSciences Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 14 January 2022
doi: 10.3389/fphar.2021.789872

Data Sources for Drug Utilization Research in Brazil—DUR-BRA Study

Lisiane Freitas Leal[1], *Claudia Garcia Serpa Osorio-de-Castro*[2], *Luiz Júpiter Carneiro de Souza*[3], *Felipe Ferre*[4], *Daniel Marques Mota*[5], *Marcia Ito*[6], *Monique Elseviers*[7], *Elisangela da Costa Lima*[8], *Ivan Ricardo Zimmernan*[9], *Izabela Fulone*[10], *Monica Da Luz Carvalho-Soares*[5] *and Luciane Cruz Lopes*[10]*

[1]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada, [2]Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, [3]Regional Management, Oswaldo Cruz Foundation, Brasília, Brazil, [4]Faculdade de Medicina, Programa de Pós-Graduação em Saúde Pública, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [5]Brazilian Health Regulatory Agency, Brasília, Brazil, [6]Professional Master's Program in Productive Systems, Centro Estadual de Educação Tecnológica Paula Souza, São Paulo, Brazil, [7]Ghent University, Ghent, Belgium, [8]Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [9]Faculdade de Ciências da Saúde Campus Darcy Ribeiro, University of Brasília, Brasília, Brazil, [10]Graduate Pharmaceutical Science, University of Sorocaba, Sao Paulo, Brazil

Background: In Brazil, studies that map electronic healthcare databases in order to assess their suitability for use in pharmacoepidemiologic research are lacking. We aimed to identify, catalogue, and characterize Brazilian data sources for Drug Utilization Research (DUR).

Methods: The present study is part of the project entitled, "Publicly Available Data Sources for Drug Utilization Research in Latin American (LatAm) Countries." A network of Brazilian health experts was assembled to map secondary administrative data from healthcare organizations that might provide information related to medication use. A multi-phase approach including internet search of institutional government websites, traditional bibliographic databases, and experts' input was used for mapping the data sources. The reviewers searched, screened and selected the data sources independently; disagreements were resolved by consensus. Data sources were grouped into the following categories: 1) automated databases; 2) Electronic Medical Records (EMR); 3) national surveys or datasets; 4) adverse event reporting systems; and 5) others. Each data source was characterized by accessibility, geographic granularity, setting, type of data (aggregate or individual-level), and years of coverage. We also searched for publications related to each data source.

Results: A total of 62 data sources were identified and screened; 38 met the eligibility criteria for inclusion and were fully characterized. We grouped 23 (60%) as automated databases, four (11%) as adverse event reporting systems, four (11%) as EMRs, three (8%) as national surveys or datasets, and four (11%) as other types. Eighteen (47%) were classified as publicly and conveniently accessible online; providing information at national level. Most of them offered more than 5 years of comprehensive data coverage, and presented data at both the individual and aggregated levels. No information about population coverage was found. Drug coding is not uniform; each data source has its own coding system, depending on the purpose of the data. At least one scientific publication was found for each publicly available data source.

OPEN ACCESS

Edited by:
Mina Tadrous,
Women's College Hospital, Canada

Reviewed by:
Talita Duarte-Salles,
Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Spain
Tassia Cristina Decimoni,
University of São Paulo, Brazil

***Correspondence:**
Luciane Cruz Lopes
luciane.lopes@prof.uniso.br

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: *05 October 2021*
Accepted: *20 December 2021*
Published: *14 January 2022*

Citation:
Leal LF, Osorio-de-Castro CGS, Souza LJCd, Ferre F, Mota DM, Ito M, Elseviers M, Lima EdC, Zimmernan IR, Fulone I, Carvalho-Soares MDL and Lopes LC (2022) Data Sources for Drug Utilization Research in Brazil—DUR-BRA Study. Front. Pharmacol. 12:789872. doi: 10.3389/fphar.2021.789872

Conclusions: There are several types of data sources for DUR in Brazil, but a uniform system for drug classification and data quality evaluation does not exist. The extent of population covered by year is unknown. Our comprehensive and structured inventory reveals a need for full characterization of these data sources.

Keywords: pharmacoepidemiology, health information systems, databases (all types), Brazil, database management systems, pharmaceutical preparations, data sources, drug utilisation research

INTRODUCTION

Drug utilization research (DUR) aims to examine patterns of medication use and adherence to treatments and to assess determinants of utilization (Godman et al., 2016; Wettermark et al., 2016) The history of DUR is described elsewhere (World Health Organization, 1993; World Health Organization, 2003b; Wettermark, 2013; Wettermark et al., 2016). Over the years, the scope of DUR has expanded; methods have improved, and the use of secondary data has increased. Nonetheless, additional work is required, particularly with regard to the quality of available data (Evans, 2012; Schneeweiss, 2019).

Secondary data that are used for pharmacoepidemiology research are usually derived from information routinely collected for administrative purposes and as part of patient care (Eriksson and Ibáñez, 2016), such as drug sales, medical billing, and prescriptions (Shalini et al., 2010). Given the cost and difficulty of primary data collection, electronic healthcare databases (EHD) are commonly used in many countries to study drug safety (Pacurariu et al., 2018). Linkage of data on medication use with diagnostic, mortality, and other health databases has become routine in Europe, North America, and Asian countries (Wettermark, 2013), but not in low- and middle-income countries, notably, in Latin America (de Castro, 1999; de Castro, 2000; World Health Organization, 2003a; Baldoni, 2011; Coelho and Santos, 2012).

While high-income countries are leveraging the use of Real-World Evidence to inform regulatory decision-making (European Medicines Agency (EMA), 2018; Health Canada, 2019; Food and Drug Administration (FDA), 2020), in Latin America initiatives are incipient and limited to few settings (Durán et al., 2016; Salas et al., 2018). In Brazil, efforts related to "open data" have improved the prospects for creating systematic approaches to the use of secondary data, not only for decision-making but also for research (Controladoria Geral da União, 2020).

Despite awareness of the value of existing databases, and observed expansion of DUR in Brazil using secondary data, a mapping of databases to evaluate their potential, as well as their characteristics and applications, has not been undertaken.

The present work aimed, therefore, to identify, catalogue, and characterize secondary data sources for DUR in Brazil.

METHODS

Design

This project was derived from the "Publicly Available Data Sources for Drug Utilization Research in Latin American (LatAm) Countries—DASDURLATAM study," which is an initiative supported by the International Society for Pharmacoepidemiology (ISPE) to make an inventory for all LatAm countries (Lopes et al., 2021).

We employed a multi-phase approach to map Brazilian data sources. A network of national health experts was assembled to prepare an initial inventory of data sources for DUR. A multidisciplinary network was established. Fourteen Brazilian researchers experts in pharmacoepidemiology and health professionals working in both academia and the government sector were invited and accepted to participate. A pharmacoepidemiology expert in European data sources for DUR joined the Brazilian team (ME). A literature review was conducted to retrieve drug utilization studies conducted in Brazil using secondary data. Finally, data sources were selected and characterized.

Type of Data Sources (Eligibility Criteria)

The eligibility criteria for inclusion in the inventory specified Brazilian data sources generated by healthcare organizations that provide information related to medication use. Data sources from health insurance companies or other commercial providers (e.g., IQVIA) were not eligible. The Brazilian health care system consists of public and private components. Population access depends on several factors, including the ability to pay for health care. We, therefore, focused on data sources generated by the public health system because:

1) The public system provides national data with municipality granularity.
2) Almost 80% of the Brazilian population is covered by the public system; private health care insurance companies are spread across the country and comprise many small companies, not representative of the general population (Paim et al., 2011; Massuda et al., 2018).
3) It is not possible to map data with no payment requests or ethical approval.

We excluded data sources in which information about medicines (names or codes) was not recorded.

Search Strategy

We conducted an internet search of institutional government websites up to January 2021. To retrieve studies, we reviewed the literature available on traditional bibliographic databases (MEDLINE/PubMed, LILACS, Google Scholar) from inception to August 2020, with no limits on publication type, status, or language. The concept terms were freely combined, using Boolean operators (AND/OR): "pharmacoepidemiology," "drug

utilization," "BRAZIL," and the acronym of the data source first identified. The Systems and Products Catalog of the Informatics Department of the Unified Health System–DataSUS (Ministério da Saúde, 2020) was also reviewed. This was done to assess the description of all systems already available through the Ministry of Health interface, and the availability of medication data recorded by the Ministry of Health, and not previously identified by the network of specialists or through the literature review.

Screening of Data Sources for Drug Utilization Research

Working in pairs and independently, the expert network (DMM, CGSOC, LCL, FF, LFL and LJCS) conducted in-depth screening and reviewed potentially eligible data sources. Disagreements on whether specific data sources contained drug information and whether they should remain on the list to be mapped as potential data source for DUR were discussed in online meetings. A consensus was achieved on the inclusion or exclusion of data sources.

Data Collection and Data Analysis

The data sources were classified and grouped into the following categories: 1) automated databases (subclassified as administrative claims data and other transactional and operational data); 2) Electronic Medical Records (EMR); 3) national surveys or datasets; 4) adverse event reporting systems; and 5) other sources, according to Harpe et al.'s classification for secondary data (Harpe, 2010) (**Supplemental Table S1**). For a general description of each data source, we used a seven-criteria checklist (Box 1). Additional information for characterizing the data sources was collected: custodian; data retrieval pathway, corresponding to the Uniform Resource Locator (URL) where the data source may be found; file format in which data are provided, that is, the way in which information is encoded for storage (comma-separated values—CSV, XLSX, ZIP, Plain Text-txt, or another format); and type of tables used for medication coding—European Article Number-EAN, Brazilian Non-proprietary Names (in Portuguese, *Denominação Comum Brasileira*—DCB), or other). Additional information was completed according to the provider's definitions and specialist consultation (FF and LJCS). Each national DUR expert was responsible for reviewing the descriptions of the data sources and their final characterization.

RESULTS

The expert network identified 62 data sources. After application of the exclusion criteria, 39 sources were included. Two of them (SIASG-*Sistema Integrado de Administração de Serviços Gerais* and SISME-*Sistema de Minuta de Empenho*) were related to the same drug-purchasing system and were grouped as one data source. Thus, the final selection consisted of 38 data sources, which underwent further characterization (**Figure 1**). Six rounds of discussion took place among the national health experts in order to achieve consensus and define the final list (**Supplementary Table S2**).

Figure 2 shows how the data sources were grouped. Twenty-three (60%) were classified as automated health care databases; four (11%) as EMRs; four (11%) as adverse event reporting systems; three (8%) as national surveys or datasets; and four (11%) as other types. The description of each data source, as well as the rationale for grouping it in a particular category, is provided in the supplementary material (**Supplementary Table S3**).

Based on the analysis of each data source, 18 (47%) were classified as "publicly and conveniently accessible online," 15 of which (88%) were accessible through the DataSUS, with the Brazilian Ministry of Health as custodian. All publicly available online data sources provided national information; most of them had more than 5 years of coverage and both individual- and aggregate-level information. Twenty data sources (53%) were known to collect individual-level data, and three (PNAUM, SIA-SUS, and SIVEP-Gripe) were available for download. **Table 1** displays the data sources, grouped by accessibility, geographic granularity, type, setting, and initial year of release. The detailed classification, which allows comparability among the data sources is provided in the supplementary material (**Supplementary Table S4**).

URLs for the "publicly and conveniently accessible online" data sources are shown in **Table 2**, as well as the file formats. The URLs for all data sources selected are provided in the supplemental material (**Supplementary Table S5**). Access through the FTP directory is provided for limited data sources and is also provided in the supplemental material (**Supplementary Table S6**).

In Brazil, six different ways of assigning codes to medicines were found. Drug coding is not uniform; each data source has its own coding system, depending on the purpose of the data. The drug coding systems employed in Brazil are shown in **Table 3**, with examples of data sources that use each system. This information was not available for all data sources, an indication of the need for further work on characterization.

The literature review was part of the initial process for mapping Brazilian databases. We found publications related to 23 of the 38 data sources, including reports, manuals, and other documents available online. Scientific articles had been published in national and in international journals. Examples of studies that used some of the selected data sources are presented in **Table 4**.

DISCUSSION

This study provides an overview of data sources that are used or have the potential to be used for DUR in Brazil. A total of 38 sources were identified, almost half of which are publicly available and provide national information. Nineteen sources collect individual-level data, but few provide it for download. Those classified as "other sources" were generally related to Ministry of Health administrative processes, as medicines purchases and prices. Further characterization to determine the types of research questions they might address is needed. In Brazil, six different ways of assigning codes to medicines are employed, none of which is recognized internationally. Brazilian data

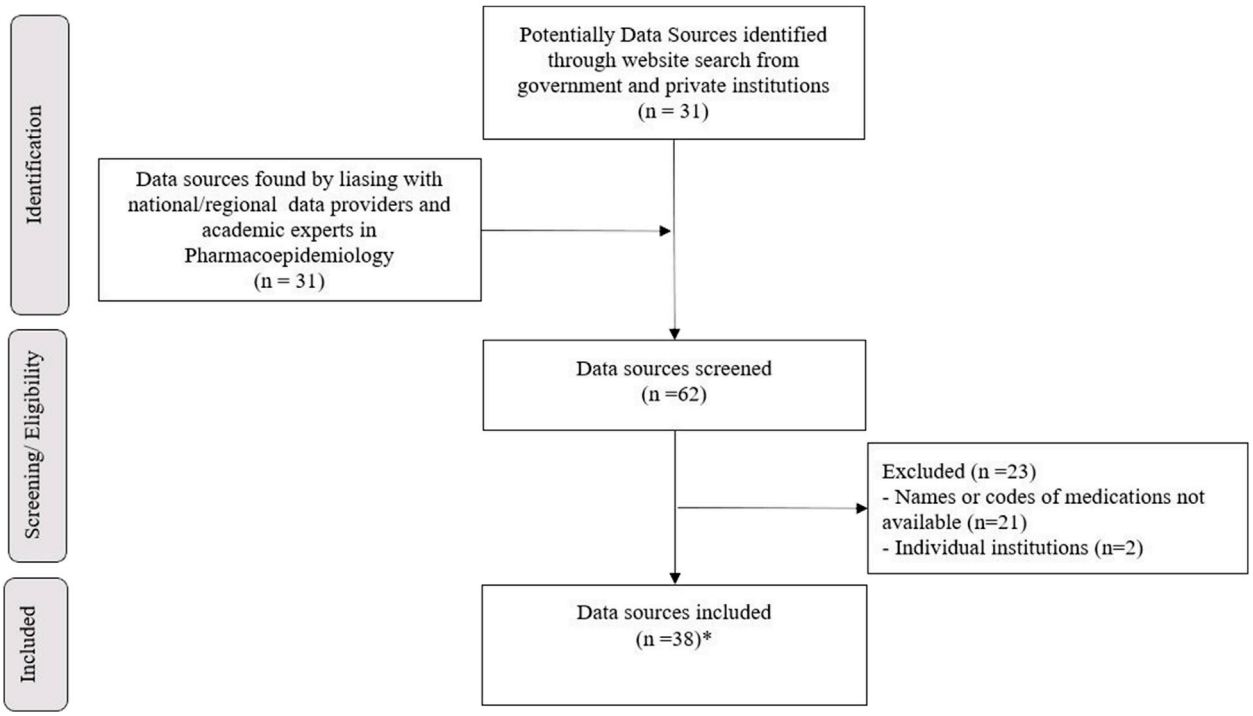


FIGURE 1 | Data sources for DUR in Brazil selection flowchart. * means third-nine data sources were selected. When characterized, two were related to the same drug-purchasing system and were grouped into one data source (SIASG and SISME).

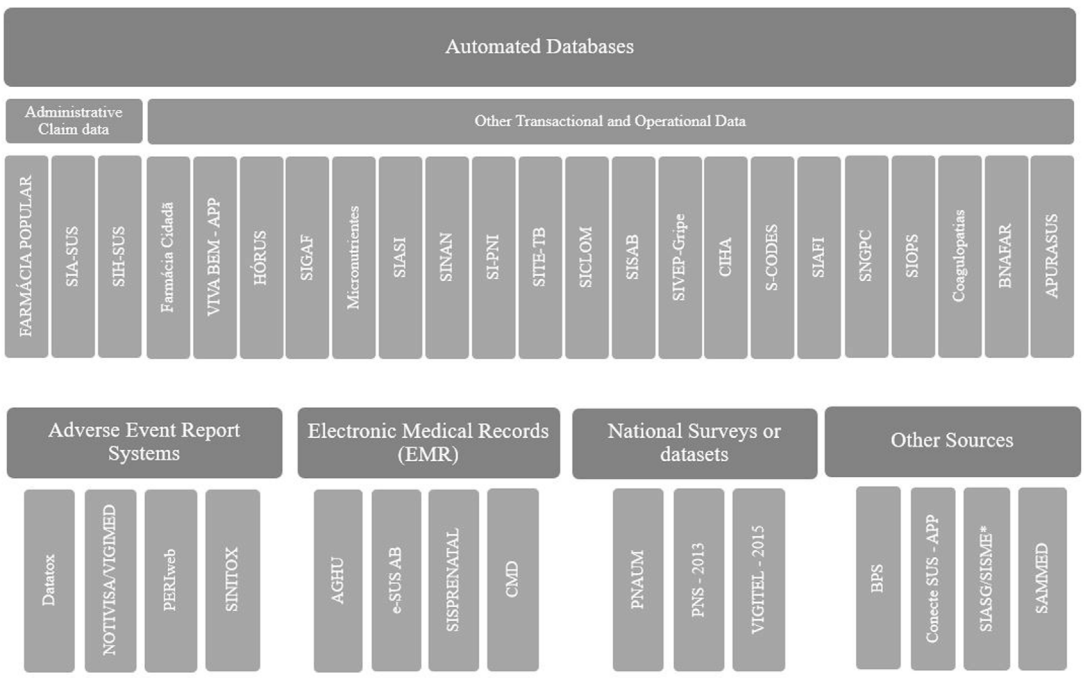


FIGURE 2 | Classification of data sources identified in Brazil.

sources have the potential to answer research questions related to medication use, adherence to treatments, purchases, and safety. However, currently mapped sources comprise a mix of databases, of unknown quality, centralized by the national government, but decentralized in terms of research and their usability and purposes for decision-making and post-market surveillance.

TABLE 1 | Selected data sources, grouped by accessibility, geographic granularity, sector, setting, and type of data.

Characteristics	Data sources (N = 38)[a]
Acessibility	
Publicly and conveniently accessible online	BPS; CIHA; CMD; Micronutrientes; PNAUM; PNS; SI-PNI; SIA-SUS; SIH-SUS; SINAN; SINITOX; SIOPS; SISAB; SISPRENATAL; Sivep-gripe; SNGPC; and Vigitel
Restricted pre-authorized protocol-only access	AGHU
Access limited to or dependent on country-specific legislation - Freedom of Information Act	CIHA; e-SUS AB; Farmácia Cidadã; FARMÁCIA POPULAR; HORUS; NOTIVISA/VIGIMED; PERIweb; SIAFI; SIASG/SISME; SIA-SUS; SICLOM; SIGAF; SIH-SUS; SINAN; SISAB; SISPRENATAL; Site-TB; Sivep-gripe; and SNGPC
Available only to researchers working in the institution (only people from the institution that provides the database)	DATATOX; PERIweb; S-CODES; SIASG/SISME; and SIGAF
The process for obtaining data is not clear, without general regulation	None
Not accessible/Data not available for public use	APURASUS; BNAFAR; COAGULOPATIAS; Conecte SUS - APP; SAMMED; SIASI; and VIVA BEM - APP
Geographic granularity	
National	APURASUS; BNAFAR; BPS; CIHA; CMD; COAGULOPATIAS; DATATOX; e-SUS AB; FARMÁCIA POPULAR; HORUS; Micronutrientes; NOTIVISA/VIGIMED; PNAUM; PNS; SI-PNI; SIAFI; SIASG/SISME; SIA-SUS; SICLOM; SIH-SUS; SINAN; SINITOX; SIOPS; SISAB; SISPRENATAL; Site-TB; Sivep-gripe; SNGPC; VIGITEL; SAMMED; and VIVA BEM - APP
Regional (province, state, more than one city)	AGHU; APURASUS; BNAFAR; CIHA; CMD; COAGULOPATIAS; Conecte SUS - APP; DATATOX; e-SUS AB; Farmácia Cidadã; FARMÁCIA POPULAR; HORUS; Micronutrientes; NOTIVISA/VIGIMED; PERIweb; PNAUM; PNS; S-CODES; SAMMED; SI-PNI; SIAFI; SIASI; SIA-SUS; SICLOM; SIGAF; SIH-SUS; SINAN; SINITOX; SIOPS; SISAB; SISPRENATAL; Site-TB; Sivep-gripe; SNGPC; VIGITEL; and VIVA BEM - APP
Municipality (one city)	None
Organization multi-sited	None
Sector of data source	
Public health system	AGHU; APURASUS; BNAFAR; CMD; COAGULOPATIAS; e-SUS AB; Farmácia Cidadã; FARMÁCIA POPULAR; HORUS; Micronutrientes; SAMMED; SIAFI; SIASG/SISME; SIASI; SIA-SUS; SICLOM; SIGAF; SIH-SUS; SISAB; SISPRENATAL; Site-TB; VIGITEL; and VIVA BEM - APP
Private sector	SNGPC
Both	BPS; CIHA; Conecte SUS - APP; DATATOX; NOTIVISA/VIGIMED; PERIweb; PNAUM; PNS; S-CODES; SAMMED; SI-PNI; SINAN; SINITOX; SIOPS; Sivep-gripe; and VIGITEL
Type of data source	
Wholesaler	None
Pharmacy records	BNAFAR; CIHA; COAGULOPATIAS; Conecte SUS - APP; Farmácia Cidadã; FARMÁCIA POPULAR; HORUS; Micronutrientes; SI-PNI; SIAFI; SIASG/SISME; SIASI; SIA-SUS; SICLOM; SIGAF; SISAB; SNGPC; and VIVA BEM - APP
Patient records	AGHU; CIHA; COAGULOPATIAS; Conecte SUS - APP; e-SUS AB; SAMMED; SIASI; SIA-SUS; SIH-SUS; SISAB; SISPRENATAL; Site-TB; and VIVA BEM - APP
Setting of data source	
Ambulatorial	BNAFAR; COAGULOPATIAS; e-SUS AB; Farmácia Cidadã; FARMÁCIA POPULAR; HORUS; Micronutrientes; SI-PNI; SIA-SUS; SIGAF; SISAB; and SNGPC
Hospital	SIH-SUS
Both	AGHU; APURASUS; CIHA; CMD; Conecte SUS - APP; NOTIVISA/VIGIMED; PERIweb; S-CODES; SAMMED; SIASI; SICLOM; SINAN; SINITOX; SIOPS; SISPRENATAL; Sivep-gripe; and VIVA BEM - APP
Type of data	
Aggregate level[b]	APURASUS; BPS; CIHA; COAGULOPATIAS; DATATOX; Micronutrientes; PNS; S-CODES; SAMMED; SI-PNI; SIAFI; SIASG/SISME; SIASI; SIA-SUS; SICLOM; SIH-SUS; SINAN; SINITOX; SIOPS; SISAB; SISPRENATAL; SNGPC; and VIGITEL

(Continued on following page)

TABLE 1 | (*Continued*) Selected data sources, grouped by accessibility, geographic granularity, sector, setting, and type of data.

Characteristics	Data sources (N = 38)[a]
Acessibility	
Individual level	AGHU; BNAFAR; CIHA; Conecte SUS - APP; e-SUS AB; Farmácia Cidadã; HORUS; Micronutrientes; NOTIVISA/VIGIMED; PERIweb; PNAUM; PNS; SIA-SUS; SIGAF; SIH-SUS; SINAN; Site-TB; Sivep-gripe; SNGPC; and VIVA BEM - APP
Years coverage	
Since	1979–2020

[a]*Data sources can be classified in more than one category within the same domain.*
[b]*Data sources that provide aggregate level data and also figure as individual level can be available for research after requesting data for custodians and/or ethical approval.*

Some of the data sources presented here had been used by researchers. Ali et al. have described the linkable databases currently available for evaluating health technology assessment in Brazil (Ali et al., 2019). For example, the CIDACS initiative uses SINAN, SIH-SUS, SINASC (Live Births Information System), and SIM (Mortality Information System) to assess outcomes of major social programs (Barreto et al., 2019). SIM (not included in our inventory because it presents only data related to ICD-10 codes for drug poisoning mortality (Mota et al., 2012)) and SINASC are important sources of data for evaluating health outcomes and indicators. The quality of data in both systems has improved over time (Szwarcwald et al., 2019; França et al., 2020); however, health outcomes of medication exposure (not related to poisoning) remain unexplored for most classes of medicines.

Junior et al. linked SIH, SIA, SIM, SINASC and SINAN (Guerra Junior et al., 2018) and created a National Database of Health for longitudinal studies. Freire et al. linked SIM and SIH, including information from APACs (Authorization of High Complexity Procedures of the Outpatient), provided by the SIA-SUS system, and were able to describe the trajectory of patients in the health care network, and cancer-related hospital admissions (Freire et al., 2015). In fact, the APAC reports are among the most important sources of information on medication dispensing in Brazil. However, the information pertains only to drugs dispensed free of charge; that is, only medications supplied by SUS under the APACs are recorded and available through DataSus systems. Moreover, the generation and consolidation of APACs to make the data available for DUR are complex. Few research groups have the expertise required to link the different data sources and prepare the data for longitudinal analysis (Soares and Silva, 2013).

Exposure to medications among the Brazilian population is complicated by the structure of health care delivery, where a private system co-exists with a public system, and no overall control is in place for dispensing most medicines. Consequently, only studies using data from APACs for biological agents, chemotherapy, and other high-cost medicines have the potential to correctly ascertain exposure (Prestes, 2017; Junior et al., 2018).

Other automated health care databases, some of which were identified by Ali et al. (Ali et al., 2019), could be valuable for DUR, but not without an extensive evaluation of the quality of the data they contain. Notable examples are *Horus, Farmacia Popular* and BNAFAR. Interfaces among the systems that generate these databases are known, but nothing is known about their quality, coverage, and completeness. These data sources, specifically the BNAFAR and the *Horus,* were not available for research (Ministério da Saúde, 2018). Infrastructure issues are familiar limitations, and at least partially explain why data on drug dispensing are so difficult to obtain in our country (Herrett et al., 2015; Hallas et al., 2017). Pharmacoepidemiology research perspectives in Brazil suffer constraints not due to lack of data, but to lack of linked data and cross-validated secondary data (de Castro, 1999; Junior et al., 2018; da Saúde, 2018).

The *Sistema Nacional de Gerenciamento de Produtos Controlados* (SNGPC) (Agência Nacional de Vigilância Sanitária, 2019), which monitors dispensing of narcotic and psychotropic medications, and since 2013, antibiotics, is an important data source for controlling the purchase and dispensing of medicines. An "open data" initiative launched by ANVISA has yielded data for DUR. The expectation is that data provided by ANVISA might allow assessing, for example, policy impact of medicines regulation. However, a complete characterization of these data sources for understanding the quality of provided data, and what research questions would be answered using the open data are still lacking.

SIVEP-Gripe and SI-PNI, among other automated health care databases (**Table 1**), record information on medication use, but the quality, temporality and feasibility for linkage of these data have not been adequately explored for DUR. SIVEP-Gripe is available and provides individual-level data, but the incompleteness of certain variables and lack of temporality in recording medication use, render the information useless for examining, for instance, the effectiveness of medication use. SIVEP-Gripe is an epidemiologic surveillance system that was designed for other purposes, but with properly recorded information, it could help answer important research questions and support other voluntary reporting systems in evaluating adverse drug effects (Melo et al., 2021). As well, non-prescription drugs recorded in surveillance systems such as SINAN, and SIVEP-Gripe are often taken during the onset of a disease—an upturn in sales may serve as an early indicator of an outbreak or epidemic (Das et al., 2005; Edge et al., 2006).

The Electronic Medical Record (EMR) of the Management Application for University Hospitals–AGHU currently covers 30 hospitals across the country (Ministério da Educação, 2019). It is the standard management system for all federal university hospitals provided by the *Empresa Brasileira de Serviços Hospitalares* (Ebserh) network and is a potential data source

TABLE 2 | Additional characteristics: path and file format available among data sources freely available online.

Data source	Custodian	Path	File Format
BPS	Ministry of Health	https://antigo.saude.gov.br/gestao-do-sus/economia-da-saude/banco-de-precos-em-saude/bases-anuais-compiladas	CSV (ZIP)
CIHA	Ministry of Health	http://ciha.datasus.gov.br/CIHA/index.php	DBC
*CMD**	Ministry of Health	http://datasus.saude.gov.br/transferencia-de-arquivos2/#; https://conjuntominimo.saude.gov.br/#/cmd; http://www2.datasus.gov.br/DATASUS/index.php?area=0901&item=1&acao=37	CSV
Micronutrientes	Ministry of Health	https://sisaps.saude.gov.br/micronutrientes/	CSV
PNAUM	Ministry of Health	http://www.ufrgs.br/pnaum	TXT (ZIP)
PNS	Ministry of Health	http://www2.datasus.gov.br/DATASUS/index.php?area = 0208&id = 28247790; https://www.ibge.gov.br/estatisticas/sociais/justica-e-seguranca.html	HTML
		https://dados.gov.br/dataset/xn-pesquisa-nacional-de-saude	DBC
		—	JSON
		—	XML
		—	ODS
SI-PNI	Ministry of Health	http://pni.datasus.gov.br/; https://datasus.saude.gov.br/acesso-a-informacao/imunizacoes-desde-1994/	XLS
SIA-SUS	Ministry of Health	http://www2.datasus.gov.br/DATASUS/index.php?area = 0901	DBC
SIH-SUS	Ministry of Health	http://www2.datasus.gov.br/DATASUS/index.php?area = 0901	DBC
SINAN	Ministry of Health	https://portalsinan.saude.gov.br/dados-epidemiologicos-sinan	CSV
		http://datasus.saude.gov.br/transferencia-de-arquivos2/#	DBC
SINITOX	Oswaldo Cruz Foundation (Fiocruz)	https://sinitox.icict.fiocruz.br/dados-regionais	PDF
SIOPS	Ministry of Health	http://siops.datasus.gov.br/relUN.php?acao = 7	HTML
SISAB	Ministry of Health	https://sisab.saude.gov.br/index.xhtml	Excel
			CSV
			ODS
SISPRENATAL	Ministry of Health	http://datasus1.saude.gov.br/sistemas-e-aplicativos/epidemiologicos/sisprenatal	DBC
		http://datasus.saude.gov.br/transferencia-de-arquivos2/#	
Sivep-gripe	Ministry of Health	http://plataforma.saude.gov.br/coronavirus/dados-abertos/	CSV
SNGPC	Brazilian Health Regulatory Agency (Anvisa)	https://dados.gov.br/dataset?q = sngpc&sort = score + desc%2C + metadata_modified + desc	CSV
VIGITEL	Ministry of Health	http://datasus.saude.gov.br/vigitel-vigilancia-de-fatores-de-risco-e-protecao-para-doencas-cronicas-por-inquerito-telefonico/	XLS
		http://svs.aids.gov.br/download/Vigitel/	

TABLE 3 | Drug coding system in Brazil.

Drug coding system	Description	Data sources
EAN-13	This is the International Article Number (also known as European Article Number or EAN). It is a standard describing a barcode symbology and numbering system used in global trade to identify a specific retail product type, in a specific packaging configuration, from a specific manufacturer. In Brazil, it presents the National Code of the Products	FARMÁCIA POPULAR; BPS
CATMAT	This is the Material Registry of the Ministry of Economy (in Portuguese, Cadastro de Materiais do Ministério da Economia). This code allows the cataloging of materials destined to the activities and means of Public Administration. The categories referring to health products and medicines are under the responsibility of the Cataloging Unit of the Ministry of Health (UC/MS). The objective is to establish and maintain a unique and standardized language for the identification, coding and description of materials to be acquired by the Federal Government, through ComprasNet.	BNAFAR; HORUS; BPS
DCB	The Common Brazilian Denomination (in Portuguese, Denominação Comum Brasileira) is the medication name according to the National List of Essential Medicines (in Portuguese, RENAME, Relação Nacional de Medicamentos Essenciais). It is the generic name (non-proprietary or non-commercial) of the drug or pharmacologically active principle, based on the official chemical name and pharmacological classification, and approved by the Thematic Technical Committee of the Brazilian Pharmacopoeia Commission (CTT-DCB), in the form of Board Resolution Anvisa Collegiate Body (RDC)	BPS; SI-PNI; SISAB; CMD
SIGTAP	This the code adopted by the System of Procedures, Medicines and OPM Management of the Unified Health System. It is known as the SUS Table (in Portuguese, *Tabela* SUS)	SIA-SUS; SIH-SUS; SISAB
Register number	This is the register number that informs the complete number by which the product is registered with *Anvisa*, including the digits related to the presentation (13 digits)	BPS
Specific codes, drug name, or active principle	Name of the medication recorded as the name of active principle or coded according to the study protocol	PNAUM; PNS; SGNPC; SINAN

TABLE 4 | Examples of DUR published using Brazilian data sources.

Title	Data source
Acesso e uso de medicamentos para hipertensão arterial no Brasil Mengue et al. (2016b)	PNAUM
Uso de medicamentos e outros produtos com finalidade terapêutica entre crianças no Brasil Pizzol et al. (2016)	
Prevalência da automedicação no Brasil e fatores associados Arrais et al. (2016)	
Utilização de anti-hipertensivos e antidiabéticos no Brasil: análise das diferenças socioeconômicas. Pesquisa Nacional de Saúde 2013 Monteiro et al. (2019)	PNS
Análise clínica e epidemiológica das internações hospitalares de idosos decorrentes de intoxicações e efeitos adversos de medicamentos, Brasil, de 2004 a 2008 Paula et al. (2012)	SINITOX; SIH-SUS
Sistema nacional de informações tóxico-farmacológicas: o desafio da padronização dos dados Santana et al. (2011)	
Bortoletto and Bochner (1999)	
*Eventos adversos notificados ao Sistema Nacional de Notificações para a Vigilância Sanitária (NOTIVISA): Brasil, estudo descritivo no período 2006 a 2011*Oliveira et al. (2013)	NOTIVISA/VIGIMED
Reações adversas a medicamentos no sistema de farmacovigilância do Brasil, 2008 a 2013: estudo descritivo Mota et al. (2019)	
Record linkage of pharmacovigilance and registration databases: a study of biological medicines in Brazil Soares and Silva (2013)	
Perfil da utilização de antimicrobianos em um hospital privado Rodrigues and Bertoldi (2010)	AGHU
Ações judiciais: estratégia da indústria farmacêutica para introdução de novos medicamentos Chieffi and Barata (2010)	S-CODES
Evaluation of a web-based registry of inherited bleeding disorders: a descriptive study of the Brazilian experience with HEMOVIDAweb Coagulopatias Rezende et al. (2017)	Coagulopatias
Quality Evaluation of Poison Control Information Systems: A Case Study of the DATATOX System Alves et al. (2016)	Datatox
Aspectos relacionados à utilização de antirretrovirais em pacientes de alta complexidade no estado do Rio de Janeiro, Brasil Madruga et al. (2018)	SICLOM
Utilização do e-SUS AB e fatores associados ao registro de procedimentos e consultas da atenção básica nos municípios brasileiros Thum et al. (2019)	SISAB
Farmácia Cidadã: Integralidade, Humanização e Racionalidade Na Atenção Ao Paciente Machado-dos-Santos (2014)	Farmácia Cidadã
Programa "Farmácia Popular do Brasil": caracterização e evolução entre 2004–2012 Silva and Caetano (2015)	FARMÁCIA POPULAR
Gastos com pagamentos no Programa Aqui Tem Farmácia Popular: evolução entre 2006–2014 Silva and Caetano (2018)	
Towards preventive pharmacovigilance through medicine misuse identification: an example with recombinant human growth hormone for aesthetic purposes Rodrigues-Neto et al. (2018)	PERIweb
Vigitel Brasil: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica do uso e fontes de obtenção dos medicamentos para tratamento da hipertensão e diabetes nas capitais dos 26 estados brasileiros e no Distrito Federal, 2011 a 2013 Ministério da Saúde (2017)	VIGITEL
Evaluation study of the National Immunization Program Information System Silva et al. (2018)	SI-PNI
Evidências advindas do consumo de medicamentos moduladores do apetite no Brasil: um estudo farmacoeconométrico Mota and Silva (2012)	SNGPC
Consumo do benzodiazepínico clonazepam (Rivotril®) no estado do Rio de Janeiro, Brasil, 2009–2013: estudo ecológico Zorzanelli et al. (2019)	
Uso de registros de assistência farmacêutica do Sistema de Informações Ambulatorial para avaliação longitudinal de utilização e adesão a medicamentos Soares and Silva (2013)	SIH/SIA-SUS
Costs in the Treatment of Schizophrenia in Adults Receiving Atypical Antipsychotics: An 11-Year Cohort in Brazil Barbosa et al. (2018)	
Ten-year kidney transplant survival of cyclosporine- or tacrolimus-treated patients in Brazil Gomes et al. (2016)	
Demographics, deaths and severity indicators in hospitalizations due to drug poisoning among children under age five in Brazil Maior et al. (2020)	
Public financing of human insulins in Brazil: 2009–2017 dos Santos Dias et al. (2020)	SIASG
Immunosuppressants in Brazil: underlying drivers of spending trends, 2010–2015 Alves et al. (2018)	

for DUR. University hospitals treat both in- and outpatients. The creation of a large cohort of patients receiving different levels of care would allow for follow-up of short- and long-term effects of medication on several outcomes. e-SUS AB might be used for the same purpose. However, no single DUR study was found to have used the Ebserh data.

We classified four data sources as adverse event report systems: NOTIVISA/VIGIMED, SINAN, SINITOX, and DATATOX. Recently, ANVISA published implementation of the VigiFlow (named Vigimed in Brazil) (Vogler et al., 2020) as a substitute for the NOTIVISA in an effort to enhance the usability of the national system. But no information is available about how different pharmacovigilance systems across the country could be integrated. In 2021, part of Vigimed aggregated data was available on the Anvisa website by drug, adverse reaction (MedDRA SOC/Preferred Term), severity, age group, gender, state of the case report, for example. Clinical trial reports are also recorded in the same database (Notivisa EC) but are not available given the need for data confidentiality.

Spontaneous reporting systems constitute a major resource for detecting adverse drug effects and have made important contributions to pharmacoepidemiology (Strom and Carson, 1990). Systems for active surveillance and projects for detecting signals and monitoring recently approved medications (Racoosin et al., 2012) have been established in other countries. Recent studies involving disproportionality analysis for safety signal screening in children (Vieira et al., 2020) and breast cancer patients (Barcelos et al., 2019) using Notivisa were conducted, demonstrating the potential of this data source. However, Brazil lags behind in terms of research initiatives and decision-making using automated administrative data.

The only national-level drug utilization study that has been conducted in Brazil was based on primary data (Mengue et al., 2016a). The National Survey on Access, Use and Promotion of Rational Use of Medicines (PNAUM) was a cross-sectional, population-based study focusing on urban households. Fieldwork was carried out between September 2013 and

February 2014. In total, 41,433 interviews were carried out. The survey examined medication use for chronic health conditions. However, the PNAUM has not been repeated, and the cross-sectional data do not allow evaluation of outcomes. Also, this was the only study to collect population-level data about over-the-counter medication use. Currently, no information about over-the-counter is available in any of the automated databases (Arrais et al., 2016). Other important surveys (cross-sectional) were included in our inventory—PNAD and Vigitel—although their purpose is to assess other characteristics of the Brazilian population and do not provide medication details.

Brazil has no formal policy on setting priorities and using administrative data to evaluate the effectiveness and safety of medications. However, many systems contain information for managing logistics and drug expenditures. APURASUS, SIGAF and SIASG are used by different levels of government to control costs and transmit information from local systems to the national level to plan acquisition and distribution. For example, SIASG made it possible to explore expenditures, pricing and judicial demands for a variety of drugs and drug classes, and it has been important for decision-making about the incorporation of drugs in the national list and the sustainability of provision programs (Luo et al., 2014; Chaves et al., 2017; Chama Borges Luz et al., 2017; Magarinos-Torres et al., 2017; dos Santos Teodoro et al., 2017; Alves et al., 2018; Caetano et al., 2020; dos Santos Dias et al., 2020, 2009–2017; Matos et al., 2020). However, the safety profile of medicines and outcomes in the population cannot be examined with these data.

Despite efforts made by the Ministry of Health to harmonize the recording of information, health institutions' data collection processes differ considerably. Because of the structure of the healthcare system, patients typically seek care from a variety of providers at several institutions with nonlinked electronic health record systems. Combining data from these systems is a challenge. One of the most important issues to emerge from this study is the lack of unique key identifiers for individuals. These factors, in addition to technological infrastructure and skilled human resource constraints, limit the usefulness of routinely collected data in generating evidence to support clinical and policy decisions and in answering epidemiological questions (Ali et al., 2019).

Another important finding is the heterogeneity of drug-coding systems in Brazil. Federal Law No. 9,787/99 requires that, within the scope of the SUS, purchases of medicines, under any type of acquisition, as well as medical and dental prescriptions for medicines, adopt the DCB (Brazilian Non-proprietary name) or, in their absence, the International Non-proprietary Name (INN). However, this does not apply to administrative databases. For each data source, it is necessary to know the types of codes that are employed, how they are constructed, and why they are used, but no clear definitions are provided.

The limitations of this inventory of Brazilian databases that contain medication-related information are mainly related to the design of the study and the difficulty of assembling a group of experts with an in-depth knowledge of each data source. We may have missed data sources and relevant studies. The literature search was conducted using the names of the data sources, but if a name was unknown, studies could not be found, and the data source was not included. Moreover, this is only an inventory; full characterization of each database has yet to be done.

The main value of this study is to provide an overview with a focus on data sources for DUR. The methodology used by the LatAm project may be highlighted as one of the main strengths of our study, an original multi-phase approach allowing to map national data sources for DUR. The next step is to fully characterize each database using pre-established checklists (Hall et al., 2012), and thereby provide information that will help researchers determine which sources may be may be useful for specific types of studies; what research questions can feasibly be addressed; how the data can be accessed; and what quality may be expected from the data.

Based on this comprehensive and structured inventory, we provided an overview of the several types of data sources for DUR in Brazil. Our findings demonstrated that a uniform system for drug classification, data quality evaluation, and the extent of population covered by year are lacking in the mapped data sources. National administrative health databases are provided mainly through the DataSus and contain information about the population covered by the SUS. Further work is required to assess the reliability of Brazilian data for DUR.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

CGSOC, LCL, ME, and LFL contributed to the conception and design of the study. LFL organized the data and wrote the first draft of the manuscript. LJCS, FF, DMM, MI, ME, ECL, IRZ, IF, and MLCS performed the review and critical analysis of the data sources. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This study is sponsored by the International Society of Pharmacoepidemiology ISPE/2018. LFL is supported by a postdoctoral scholarship award from the Fonds de recherche du Québec–Santé (FRQS; Quebec Foundation for Health Research) in parternership with Société québécoise d'hypertension artérielle (SQHA) — Dossier:290908

(2020–2021); and by a CIHR Drug Safety and Effectiveness Cross-Disciplinary Training Program (DSECT)— trainee funding Stream 1 (2021–2022).

ACKNOWLEDGMENTS

The authors acknowledge the International Society for Pharmacoepidemiology for supporting the Publicly Available Data Sources for Drug Utilization Research in Latin American (LatAm) Countries—DASDURLATAM study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.789872/full#supplementary-material

REFERENCES

Agência Nacional de Vigilância Sanitária (2019). Sistema Nacional de Gerenciamento de Produtos Controlados (SNGPC). Available at: http://portal.anvisa.gov.br/produtos_controlados (Accessed June 24, 2019).

Ali, M. S., Ichihara, M. Y., Lopes, L. C., Barbosa, G. C. G., Pita, R., Carreiro, R. P., et al. (2019). Administrative Data Linkage in Brazil: Potentials for Health Technology Assessment. *Front. Pharmacol.* 10, 984. doi:10.3389/fphar.2019.00984

Alves, J. C., Osorio-de-Castro, C. G. S., Wettermark, B., and Luz, T. C. B. (2018). Immunosuppressants in Brazil: Underlying Drivers of Spending Trends, 2010-2015. *Expert Rev. Pharmacoecon Outcomes Res.* 18, 565–572. doi:10.1080/14737167.2018.1485098

Alves, J. M., Albino, D. B. L., Resener, M. C., Zannin, M., Savaris, A., von Wangenheim, C. G., et al. (2016). "Quality Evaluation of Poison Control Information Systems: A Case Study of the DATATOX System," in 2016 IEEE 29th International Symposium on Computer-Based Medical Systems (CBMS), Belfast and Dublin, Ireland, 20-24 June 2016 (IEEE), 30–35. doi:10.1109/CBMS.2016.53

Arrais, P. S. D., Fernandes, M. E., Pizzol, T., Ramos, L. R., Mengue, S. S., Luiza, V. L., et al. (2016). Prevalence of Self-Medication in Brazil and Associated Factors. *Rev. Saude Publica* 50, 13s. doi:10.1590/s1518-8787.2016050006117

Baldoni, A. (2011). A Farmacoepidemiologia No Brasil: Estado Da Arte Da Produção Científica. *Ruvrv* 9, 78–88. doi:10.5892/RUVRV.91.7888

Barbosa, W. B., Costa, J. O., de Lemos, L. L. P., Gomes, R. M., de Oliveira, H. N., Ruas, C. M., et al. (2018). Costs in the Treatment of Schizophrenia in Adults Receiving Atypical Antipsychotics: An 11-Year Cohort in Brazil. *Appl. Health Econ. Health Pol.* 16, 697–709. doi:10.1007/s40258-018-0408-4

Barcelos, F. C., de Matos, G. C., de Silva, M. J. S., da Silva, F. A. B., and da Silva, E. D. C. (2019). Suspected Adverse Drug Reactions Related to Breast Cancer Chemotherapy: Disproportionality Analysis of the Brazilian Spontaneous Reporting System. *Front. Pharmacol.* 10, 498. doi:10.3389/fphar.2019.00498

Barreto, M. L., Ichihara, M. Y., Almeida, B. A., Barreto, M. E., Cabral, L., Fiaccone, R. L., et al. (2019). The Centre for Data and Knowledge Integration for Health (CIDACS): Linking Health and Social Data in Brazil. *Int. J. Popul. Data Sci.* 4, 1140. doi:10.23889/ijpds.v4i2.1140

Bortoletto, M. É., and Bochner, R. (1999). Impacto Dos Medicamentos Nas Intoxicações Humanas No Brasil. *Cad. Saúde Pública* 15, 859–869. doi:10.1590/S0102-311X1999000400020

Caetano, R., Rodrigues, P. H. A., Corrêa, M. C. V., Villardi, P., and Osorio-de-Castro, C. G. S. (2020). The Case of Eculizumab: Litigation and Purchases by the Brazilian Ministry of Health. *Rev. Saude Publica* 54, 22. doi:10.11606/s1518-8787.2020054001693

Chama Borges Luz, T., Garcia Serpa Osorio-de-Castro, C., Magarinos-Torres, R., and Wettermark, B. (2017). Trends in Medicines Procurement by the Brazilian Federal Government from 2006 to 2013. *PLoS ONE* 12, e0174616. doi:10.1371/journal.pone.0174616

Chaves, G. C., Osorio-de-Castro, C. G. S., and Oliveira, M. A. (2017). Compras públicas de medicamentos para hepatite C no Brasil no período de 2005 a 2015. *Ciênc. Saúde Coletiva* 22, 2527–2538. doi:10.1590/1413-81232017228.05602017

Chieffi, A. L., and Barata, R. d. C. B. (2010). Ações judiciais: estratégia da indústria farmacêutica para introdução de novos medicamentos. *Rev. Saúde Pública* 44, 421–429. doi:10.1590/S0034-89102010000300005

Coelho, H. L. L., and Santos, D. B. (2012). "Farmacoepidemiologia," in *Epidemiologia & Saúde - Fundamentos, Métodos e Aplicações* (Rio de Janeiro: Guanabara Koogan), 670–677.

Controladoria Geral da União (2020). Portal Brasileiro de Dados Abertos. Available at: https://dados.gov.br/(Accessed August 11, 2021).

Das, D., Metzger, K., Heffernan, R., Balter, S., Weiss, D., Mostashari, F., et al. (2005). Monitoring Over-the-counter Medication Sales for Early Detection of Disease Outbreaks--New York City. *MMWR Suppl.* 54, 41–46.

de Castro, C. G. S. O. (2000). *Estudos de utilização de medicamentos: noções básicas*. Rio de Janeiro, RJ: Editora Fiocruz.

de Castro, L. L. C. (1999). Farmacoepidemiologia no Brasil: evolução e perspectivas. *Ciênc. Saúde Coletiva* 4, 405–410. doi:10.1590/S1413-81231999000200014

dos Santos Dias, L. L., Santos, M. A. B. D., and Osorio-de-Castro, C. G. S. (2020). Public Financing of Human Insulins in Brazil: 2009-2017. *Rev. Bras. Epidemiol.* 23, e200075. doi:10.1590/1980-549720200075

dos Santos Teodoro, C. R., Caetano, R., Godman, B., dos Reis, A. L. A., Maia, A. A., Ramos, M. C. B., et al. (2017). Federal Procurement of Unlicensed Medicines in Brazil; Findings and Implications. *Expert Rev. Pharmacoecon Outcomes Res.* 17, 607–613. doi:10.1080/14737167.2017.1311209

Durán, C. E., Christiaens, T., Acosta, Á., and Vander Stichele, R. (2016). Systematic Review of Cross-National Drug Utilization Studies in Latin America: Methods and Comparability. *Pharmacoepidemiol. Drug Saf.* 25, 16–25. doi:10.1002/pds.3896

Edge, V. L., Pollari, F., Ng, L. K., Michel, P., McEwen, S. A., Wilson, J. B., et al. (2006). Syndromic Surveillance of Norovirus Using Over-the-counter Sales of Medications Related to Gastrointestinal Illness. *Can. J. Infect. Dis. Med. Microbiol.* 17, 235–241. doi:10.1155/2006/958191

Eriksson, I., and Ibáñez, L. (2016). "Secondary Data Sources for Drug Utilization Research," in *Drug Utilization Research*. Editors M. Elseviers, B. Wettermark, A. B. Almarsdóttir, M. Andersen, R. Benko, M. Bennie, et al. (Chichester, UK: John Wiley & Sons), 39–48. doi:10.1002/9781118949740.ch4

European Medicines Agency (EMA) (2018). Scientific Guidance on post-authorisation Efficacy Studies. Eur. Medicines Agency. Available at: https://www.ema.europa.eu/en/scientific-guidance-post-authorisation-efficacy-studies (Accessed January 26, 2021).

Evans, S. J. (2012). An Agenda For UK Clinical Pharmacology: Pharmacoepidemiology: Commentary. *Br. J. Clin. Pharmacol.* 73, 973–978. doi:10.1111/j.1365-2125.2012.04248.x

Food and Drug Administration (FDA) (2020). 21st Century Cures Act. FDA. Available at: https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act (Accessed January 26, 2021).

França, E., Ishitani, L. H., Teixeira, R., Duncan, B. B., Marinho, F., and Naghavi, M. (2020). Changes in the Quality of Cause-Of-Death Statistics in Brazil: Garbage Codes Among Registered Deaths in 1996-2016. *Popul. Health Metr* 18, 20. doi:10.1186/s12963-020-00221-4

Freire, S. M., Souza, R. C. d., and Almeida, R. T. d. (2015). Integrating Brazilian Health Information Systems in Order to Support the Building of Data Warehouses. *Res. Biomed. Eng.* 31, 196–207. doi:10.1590/2446-4740.0666

Godman, B., Kwon, H. Y., Bennie, M., and Almarsdóttir, A. B. (2016). "Drug Utilization and Health Policy," in *Drug Utilization Research*. Editors M. Elseviers, B. Wettermark, A. B. Almarsdóttir, M. Andersen, R. Benko, M. Bennie, et al. (Chichester, UK: John Wiley & Sons), 203–209. doi:10.1002/9781118949740.ch19

Gomes, R. M., Guerra Júnior, A. A., Lemos, L. L., Costa, J. O., Almeida, A. M., Alvares, J., et al. (2016). Ten-year Kidney Transplant Survival of Cyclosporine-

or Tacrolimus-Treated Patients in Brazil. *Expert Rev. Clin. Pharmacol.* 9, 991–999. doi:10.1080/17512433.2016.1190270

Guerra Junior, A. A., Pereira, R. G., Gurgel, E. I., Cherchiglia, M., Dias, L. V., Ávila, J., et al. (2018). Building the National Database of Health Centred on the Individual: Administrative and Epidemiological Record Linkage - Brazil, 2000-2015. *Int. J. Popul. Data Sci.* 3 (1), 446. doi:10.23889/ijpds.v3i1.446

Hall, G. C., Sauer, B., Bourke, A., Brown, J. S., Reynolds, M. W., LoCasale, R., et al. (2012). Guidelines for Good Database Selection and Use in Pharmacoepidemiology Research. *Pharmacoepidemiol. Drug Saf.* 21, 1–10. doi:10.1002/pds.2229

Hallas, J., Hellfritzsch, M., Rix, M., Olesen, M., Reilev, M., and Pottegård, A. (2017). Odense Pharmacoepidemiological Database: A Review of Use and Content. *Basic Clin. Pharmacol. Toxicol.* 120, 419–425. doi:10.1111/bcpt.12764

Harpe, S. E. (2010). "4 Using Secondary Data in Pharmacoepidemiology," in *Understanding Pharmacoepidemiology* (New York, USA: McGraw-Hill Professional Publishing), 55–78.

Health Canada (2019). Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making. Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html (Accessed January 26, 2021).

Herrett, E., Gallagher, A. M., Bhaskaran, K., Forbes, H., Mathur, R., van Staa, T., et al. (2015). Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int. J. Epidemiol.* 44, 827–836. doi:10.1093/ije/dyv098

Lopes, L. C., Salas, M., Osorio-de-Castro, C. G. S., Leal, L. F., Doubova, S. V., Cañás, M., et al. (2021). Data Sources for Drug Utilization Research in Latin American countries - A Cross-National study: DASDUR-LATAM Study. *Pharmacoepidemiol Drug Saf.* doi:10.1002/pds.5404

Luo, J., Oliveira, M. A., Ramos, M. B., Maia, A., and Osorio-de-Castro, C. G. (2014). Antiretroviral Drug Expenditure, Pricing and Judicial Demand: an Analysis of Federal Procurement Data in Brazil from 2004-2011. *BMC Public Health* 14, 367. doi:10.1186/1471-2458-14-367

Machado-dos-Santos, S. C. (2014). "Farmácia cidadã: integralidade, humanização e racionalidade na atenção ao paciente," in *Assistência farmacêutica: gestão e prática para profissionais da saúde* (Rio de Janeiro: Editora Fiocruz), 407–416.

Madruga, L. G. d. S. L., da Silva, G. V. V., Alves, V. A. R., Velarde, L. G. C., Azeredo, T. B., Setúbal, S., et al. (2018). Aspectos relacionados à utilização de antirretrovirais em pacientes de alta complexidade no estado Do Rio de Janeiro, Brasil. *Ciênc. Saúde Coletiva* 23, 3649–3662. doi:10.1590/1413-812320182311.24742016

Magarinos-Torres, R., Lynd, L. D., Luz, T. C. B., Marques, P. E. P. C., and Osorio-de-Castro, C. G. S. (2017). Essential Medicines List Implementation Dynamics: A Case Study Using Brazilian Federal Medicines Expenditures. *Basic Clin. Pharmacol. Toxicol.* 121, 181–188. doi:10.1111/bcpt.12783

Maior, M. d. C. L. S., Osorio-de-Castro, C. G. S., and de Andrade, C. L. T. (2020). Demografia, óbitos e indicadores de agravamento nas internações por intoxicações medicamentosas entre menores de 5 anos no Brasil. *Rev. Bras. Epidemiol.* 23, e200016. doi:10.1590/1980-549720200016

Massuda, A., Hone, T., Leles, F. A. G., de Castro, M. C., and Atun, R. (2018). The Brazilian Health System at Crossroads: Progress, Crisis and Resilience. *BMJ Glob. Health* 3, e000829. doi:10.1136/bmjgh-2018-000829

Matos, C. A., Osorio-de-Castro, C. G. S., Coimbra Jr., C. E. A., Jr., and Silva, M. J. S. d. (2020). Perfil de utilização de medicamentos antineoplásicos entre indígenas atendidos pelo Sistema Único de Saúde. *Cad. Saúde Pública* 36, e00100520. doi:10.1590/0102-311x00100520

Melo, J. R. R., Duarte, E. C., de Moraes, M. V., Fleck, K., do Nascimento e Silva, A. S., and Arrais, P. S. D. (2021). Reações adversas a medicamentos em pacientes com COVID-19 no Brasil: análise das notificações espontâneas Do sistema de farmacovigilância brasileiro. *Cad. Saúde Pública* 37, e00245820. doi:10.1590/0102-311x00245820

Mengue, S. S., Bertoldi, A. D., Boing, A. C., Tavares, N. U., Pizzol, T. D., Oliveira, M. A., et al. (2016a). National Survey on Access, Use and Promotion of Rational Use of Medicines (PNAUM): Household Survey Component Methods. *Rev. Saude Publica* 50, 4s. doi:10.1590/s1518-8787.2016050006156

Mengue, S. S., Bertoldi, A. D., Ramos, L. R., Farias, M. R., Oliveira, M. A., Tavares, N. U., et al. (2016b). Access to and Use of High Blood Pressure Medications in Brazil. *Rev. Saude Publica* 50, 8s. doi:10.1590/s1518-8787.2016050006154

Ministério da Educação (2019). Empresa Brasileira de Serviços Hospitalares (Ebserh). Available at: https://www.ebserh.gov.br/inicio (Accessed June 24, 2019).

Ministério da Saúde (2020). Sistemas – DATASUS. Available at: https://datasus.saude.gov.br/sistemas/(Accessed January 26, 2021).

Ministério da Saúde (2017). *Vigitel Brasil 2015 Saúde Suplementar: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico*Available at: http://bvsms.saude.gov.br/bvs/publicacoes/vigitel_brasil_2015.pdf(Accessed December 9, 2021).

Ministério da Saúde (2018). Assistência Farmacêutica no SUS: 20 anos de políticas e propostas para o desenvolvimento e qualificação - Relatório com análise e recomendações de gestores, especialistas e representantes sa sociedade civil organizada. Available at: http://bvsms.saude.gov.br/publicacoes/assistencia_farmaceutica_sus_relatorio_recomendacoes.pdf (Accessed February 4, 2019).

Monteiro, C. N., Lima, M. G., Szwarcwald, C. L., Bastos, T. F., and Barros, M. B. d. A. (2019). Utilização de anti-hipertensivos e antidiabéticos no Brasil: análise das diferenças socioeconômicas. Pesquisa Nacional de Saúde 2013. *Rev. Bras. Epidemiol.* 22, E190014. doi:10.1590/1980-549720190014.supl.2

Mota, D. M., Melo, J. R. R., Freitas, D. R. C. d., and Machado, M. (2012). Perfil da mortalidade por intoxicação com medicamentos no Brasil, 1996-2005: retrato de uma década. *Ciênc. Saúde Coletiva* 17, 61–70. doi:10.1590/S1413-81232012000100009

Mota, D. M., and Silva, G. G. (2012). Evidências advindas do consumo de medicamentos moduladores Do apetite no Brasil: um estudo farmacoeconométrico. *Revista da Associação Médica Brasileira* 58, 88–94. doi:10.1590/S0104-42302012000100020

Mota, D. M., Vigo, Á., and Kuchenbecker, R. d. S. (2019). Reações adversas a medicamentos no sistema de farmacovigilância do Brasil, 2008 a 2013: estudo descritivo. *Cad. Saúde Pública* 35, e00148818. doi:10.1590/0102-311x00148818

Oliveira, J. R. d., Xavier, R. M. F., and Santos Júnior, A. d. F. (2013). Eventos adversos notificados ao Sistema Nacional de Notificações para a Vigilância Sanitária (NOTIVISA): Brasil, estudo descritivo no período 2006 a 2011. *Epidemiol. Serv. Saúde* 22, 671–678. doi:10.5123/S1679-49742013000400013

Pacurariu, A., Plueschke, K., McGettigan, P., Morales, D. R., Slattery, J., Vogl, D., et al. (2018). Electronic Healthcare Databases in Europe: Descriptive Analysis of Characteristics and Potential for Use in Medicines Regulation. *BMJ Open* 8, e023090. doi:10.1136/bmjopen-2018-023090

Paim, J., Travassos, C., Almeida, C., Bahia, L., and Macinko, J. (2011). The Brazilian Health System: History, Advances, and Challenges. *Lancet* 377, 1778–1797. doi:10.1016/S0140-6736(11)60054-8

Paula, T. C. d., Bochner, R., and Montilla, D. E. R. (2012). Análise clínica e epidemiológica das internações hospitalares de idosos decorrentes de intoxicações e efeitos adversos de medicamentos, Brasil, de 2004 a 2008. *Rev. Bras. Epidemiol.* 15, 828–844. doi:10.1590/S1415-790X2012000400014

Pizzol, T. D., Tavares, N. U., Bertoldi, A. D., Farias, M. R., Arrais, P. S., Ramos, L. R., et al. (2016). Use of Medicines and Other Products for Therapeutic Purposes Among Children in Brazil. *Rev. Saude Publica* 50, 12s. doi:10.1590/s1518-8787.2016050006115

Prestes, I. V. (2017). Pareamento de registros das grandes bases Do SUS para permitir análises longitudinais de pacientes com câncer. Available at: http://hdl.handle.net/10183/179058 (Accessed May 13, 2019).

Racoosin, J. A., Robb, M. A., Sherman, R. E., and Woodcock, J. (2012). "FDA's Sentinel Initiative: Active Surveillance to Identify Safety Signals," in *Pharmacoepidemiology*. Editors B. L. Strom, S. E. Kimmel, and S. Hennessy (Hoboken, NJ: Wiley-Blackwell), 534–554.

Rezende, S. M., Rodrigues, S. H., Brito, K. N., da Silva, D. L., Santo, M. L., Simões, B. J., et al. (2017). Evaluation of a Web-Based Registry of Inherited Bleeding Disorders: a Descriptive Study of the Brazilian Experience with HEMOVIDAweb Coagulopatias. *Orphanet J. Rare Dis.* 12, 27. doi:10.1186/s13023-016-0560-6

Rodrigues, F. d. A., and Bertoldi, A. D. (2010). Perfil da utilização de antimicrobianos em um hospital privado. *Ciênc. Saúde Coletiva* 15, 1239–1247. doi:10.1590/S1413-81232010000700033

Rodrigues-Neto, A. J., Biazoni-Albaricci, C., Ribeiro, A., Lima, S., and Figueras, A. (2018). Towards Preventive Pharmacovigilance through Medicine Misuse Identification: an Example with Recombinant Human Growth Hormone for Aesthetic Purposes. *Eur. J. Clin. Pharmacol.* 74, 1471–1474. doi:10.1007/s00228-018-2510-9

Salas, M., Lopes, L. C., Godman, B., Truter, I., Hartzema, A. G., Fadare, J., et al. (2018). "Challenges and Issues in Drug Utilization Research Identified from the Latin American and African Regions," in 34th International Conference on Pharmacoepidemiology and Therapeutic Risk Management 2018 (Prague, Czech Republic: Prague Congress Centre). Available at: https://strathprints.strath.ac.uk/63989/(Accessed May 10, 2019).

Santana, R. A. L. d., Bochner, R., and Guimarães, M. C. S. (2011). Sistema nacional de informações tóxico-farmacológicas: o desafio da padronização dos dados. *Ciênc. Saúde Coletiva* 16, 1191–1200. doi:10.1590/S1413-81232011000700051

Schneeweiss, S. (2019). Real-World Evidence of Treatment Effects: The Useful and the Misleading. *Clin. Pharmacol. Ther.* 106, 43–44. doi:10.1002/cpt.1405

Shalini, S., Ravichandran, V., Saraswathi, R., Mohanty, B. K., and Dhanaraj, S. K. (2010). Drug Utilization Studies – an Overview. *PCI- Approved-IJPSN* 3. Available at: https://ijpsnonline.com/index.php/ijpsn/article/view/470 (Accessed August 6, 2020).

Silva, B. S., Coelho, H. V., Cavalcante, R. B., Oliveira, V. C., and Guimarães, E. A. A. (2018). Evaluation Study of the National Immunization Program Information System. *Rev. Bras. Enferm.* 71, 615–624. doi:10.1590/0034-7167-2017-0601

Silva, R. M. d., and Caetano, R. (2018). Gastos com pagamentos no Programa Aqui Tem Farmácia Popular: evolução entre 2006-2014. *Physis: Revista de Saúde Coletiva* 28 (1), e280105. doi:10.1590/s0103-73312018280105

Silva, R. M. d., and Caetano, R. (2015). Programa "Farmácia Popular Do Brasil": caracterização e evolução entre 2004-2012. *Ciênc. Saúde Coletiva* 20, 2943–2956. doi:10.1590/1413-812320152010.17352014

Soares, C., and Silva, G. A. (2013). Uso de registros de assistência farmacêutica Do Sistema de Informações Ambulatorial para avaliação longitudinal de utilização e adesão a medicamentos. *Cad. Saúde Colet.* 21, 245–252. doi:10.1590/S1414-462X2013000300003

Strom, B. L., and Carson, J. L. (1990). Use Of Automated Databases For Pharmacoepidemiology Research. *Epidemiol. Rev.* 12, 87–107. doi:10.1093/oxfordjournals.epirev.a036064

Szwarcwald, C. L., do Carmo Leal, M., Esteves-Pereira, A. P., da Silva de Almeida, W., de Frias, P. G., Damacena, G. N., et al. (2019). Avaliação das informações Do Sistema de Informações sobre Nascidos Vivos (SINASC), Brasil. *Cad. Saúde Pública* 35, e00214918. doi:10.1590/0102-311x00214918

Thum, M. A., Baldisserotto, J., and Celeste, R. K. (2019). Utilização Do e-SUS AB e fatores associados ao registro de procedimentos e consultas da atenção básica nos municípios brasileiros. *Cad. Saúde Pública* 35, e00029418. doi:10.1590/0102-311x00029418

Vieira, J. M. L., de Matos, G. C., da Silva, F. A. B., Bracken, L. E., Peak, M., and Lima, E. D. C. (2020). Serious Adverse Drug Reactions and Safety Signals in Children: A Nationwide Database Study. *Front. Pharmacol.* 11, 964. doi:10.3389/fphar.2020.00964

Vogler, M., Ricci Conesa, H., de Araújo Ferreira, K., Moreira Cruz, F., Simioni Gasparotto, F., Fleck, K., et al. (2020). Electronic Reporting Systems in Pharmacovigilance: The Implementation of VigiFlow in Brazil. *Pharmaceut Med.* 34, 327–334. doi:10.1007/s40290-020-00349-6

Wettermark, B. (2013). The Intriguing Future of Pharmacoepidemiology. *Eur. J. Clin. Pharmacol.* 69 (Suppl. 1), 43–51. doi:10.1007/s00228-013-1496-6

Wettermark, B., Elseviers, M., Almarsdóttir, A. B., Andersen, M., Benko, R., Bennie, M., et al. (2016). "Introduction to Drug Utilization Research," in *Drug Utilization Research*. Editors M. Elseviers, B. Wettermark, A. B. Almarsdóttir, M. Andersen, R. Benko, M. Bennie, et al. (Chichester, UK: John Wiley & Sons), 1–12. doi:10.1002/9781118949740.ch1

World Health Organization (1993). *Drug Utilization Studies: Methods and Uses*. Copenhagen: World Health Organization, Regional Office for Europe. Available at: https://apps.who.int/iris/handle/10665/260517.

World Health Organization (2003a). Essential Drugs Monitor No. 032, Drug Utilization in Latin America - the Example of DURG-LA. Available at: https://digicollections.net/medicinedocs/#d/s4940e (Accessed January 26, 2021).

World Health Organization (2003b). *Introduction to Drug Utilization Research*. Geneva: World Health Organization.

Zorzanelli, R. T., Giordani, F., Guaraldo, L., Matos, G. C. d., Brito Junior, A. G. d., Oliveira, M. G. d., et al. (2019). Consumo do benzodiazepínico clonazepam (Rivotril) no estado Do Rio de Janeiro, Brasil, 2009-2013: estudo ecológico. *Ciênc. Saúde Coletiva* 24, 3129–3140. doi:10.1590/1413-81232018248.23232017

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

GLOSSARY

(alphabetic order, Portuguese acronyms and names)

AGHU: Aplicativo de Gestão para Hospitais Universitários

APURASUS: Sistema de Apuração e Gestão de Custos do SUS

BNAFAR: Base Nacional de Dados de Ações e Serviços da Assistência Farmacêutica no SUS

BPS: Banco de Preços em Saúde

CIHA: Sistema de Comunicação de Informação Hospitalar e Ambulatorial

CMD: Conjunto Mínimo de Dados

Datatox: Sistema Brasileiro de Dados de Intoxicações

e-SUS AB: e-SUS Atenção Básica

HÓRUS: Sistema Nacional de Gestão da Assistência Farmacêutica

NOTIVISA/VIGIMED: Sistema de Notificação em Vigilância Sanitária

PERIweb Sistema de Notificação Espontânea de Suspeita de Reação Adversa a Medicamento ou Desvio da Qualidade de Medicamento do Estado de São Paulo

PNAU Pesquisa Nacional sobre Acesso, Utilização e Promoção do Uso Racional de Medicamentos no Brasil

PNS Pesquisa Nacional de Saúde

S-CODES Sistema de Coordenação de Demandas Estratégicas–SP

SAMMED Sistema de Acompanhamento do Mercado de Medicamentos

SIAFI WebService Sistema Integrado de Administração Financeira

SIASG/SISME Sistema Integrado de Administração de Serviços Gerais/ Sistema de Minuta de Empenho

SIASI Sistema de Informação da Atenção da Saúde Indígena

SIA-SUS Sistema de Informações Ambulatoriais do SUS

SICLOM Sistema Gerencial de Controle Logístico de Medicamentos

SIGAF Sistema Integrado de Gerenciamento da Assistência Farmacêutica

SIH-SUS Sistema de Informação Hospitalar

SINAN Sistema de Informação de Agravos de Notificação

SINITOX Sistema Nacional de Informações Tóxico-Farmacológicas

SIOPS Sistema de Informações sobre Orçamentos Públicos em saúde

SI-PNI Sistema de Informações do Programa Nacional de Imunizações

SISAB Sistema de Informação em Saúde para a Atenção Básica

SISPRENATAL Sistema de acompanhamento do programa de humanização no pré natal e nascimento

SITE-TB Sistema de Informação de Tratamentos Especiais de Tuberculose

SIVEP-Gripe Sistema de informação de vigilância epidemiológica da gripe

SNGPC Sistema Nacional de Gerenciamento de Produtos Controlados

VIGITEL Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 07 March 2022
doi: 10.3389/fphar.2022.834898

Prior Cardiovascular Treatments—A Key Characteristic in Determining Medication Adherence After an Acute Myocardial Infarction

Anna Campain[1,2], Carinna Hockham[3], Louisa Sukkar[1,4], Kris Rogers[1,2,5], Clara K Chow[1,6,7], Thomas Lung[1,2,4], Min Jun[1,2], Carol Pollock[8,9], Alan Cass[10], David Sullivan[11,12,13], Elizabeth Comino[2], David Peiris[1,2†] and Meg Jardine[4,14,15†]*

[1]The George Institute for Global Heath, UNSW, Sydney, NSW, Australia, [2]Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia, [3]School of Public Health, Imperial College London, The George Institute for Global Health, London, United Kingdom, [4]Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia, [5]Graduate School of Health, University of Technology Sydney, Sydney, NSW, Australia, [6]Westmead Applied Research Centre, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia, [7]Department of Cardiology, Westmead Hospital, Sydney, NSW, Australia, [8]Renal Division, Kolling Institute for Medical Research, Sydney, NSW, Australia, [9]University of Sydney, Sydney, NSW, Australia, [10]Menzies School of Health Research, Charles Darwin University, Darwin, NT, Australia, [11]Department of Chemical Pathology Royal Prince Alfred Hospital, Camperdown, NSW, Australia, [12]NSW Health Pathology, Newcastle, NSW, Australia, [13]Central Clinical School, University of Sydney, Camperdown, NSW, Australia, [14]NHMRC Clinical Trials Centre, The University of Sydney, Sydney, NSW, Australia, [15]Concord Repatriation General Hospital, Sydney, NSW, Australia

OPEN ACCESS

Edited by:
Andrea Burden,
ETH Zürich, Switzerland

Reviewed by:
Esayas Kebede Gudina,
Jimma University, Ethiopia
Stefan Weiler,
ETH Zürich, Switzerland

***Correspondence:**
Anna Campain
acampain@georgeinstitute.org.au

[†]These authors have contributed equally to this work and share senior authorship

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: 13 December 2021
Accepted: 15 February 2022
Published: 07 March 2022

Citation:
Campain A, Hockham C, Sukkar L, Rogers K, Chow CK, Lung T, Jun M, Pollock C, Cass A, Sullivan D, Comino E, Peiris D and Jardine M (2022) Prior Cardiovascular Treatments—A Key Characteristic in Determining Medication Adherence After an Acute Myocardial Infarction. Front. Pharmacol. 13:834898. doi: 10.3389/fphar.2022.834898

Objective: To investigate long-term adherence to guideline-recommended cardioprotective medications following hospitalization for an acute myocardial infarction (AMI), and identify characteristics associated with adherence.

Methods: An Australian population-based cohort study was used to identify participants who had their first AMI between 2006 and 2014 and were alive after 12 months. Linked routinely collected hospital, and prescription medication claims data was used to study adherence over time. Predictors and rates of adherence to both lipid-lowering medication and renin-angiotensin system blockade at 12 months post-AMI was assessed.

Results: 14,200 people (mean age 69.9 years, 38.7% female) were included in our analysis. At 12 months post-AMI, 29.5% (95% CI: 28.8–30.3%) of people were adherent to both classes of medication. Individuals receiving treatment with both lipid-lowering medication and renin-angiotensin system blockade during the 6 months prior to their AMI were over 9 times more likely to be adherent to both medications at 12 months post-AMI (66.2% 95% CI: 64.8–67.5%) compared to those with no prior medication use (treatment naïve) (7.1%, 95% CI: 6.4–7.9%). Prior cardiovascular treatment was the strongest predictor of long-term adherence even after adjusting for age, sex, education and income.

Conclusions: Despite efforts to improve long-term medication adherence in patients who have experienced an acute coronary event, considerable gaps remain. Of particular concern are people who are commencing guideline-recommended cardioprotective medication at the time of their AMI. The relationship between prior cardiovascular treatments and post AMI adherence offers insight into the support needs for the

patient. Health care intervention strategies, strengthened by enabling policies, are needed to provide support to patients through the initial months following their AMI.

Keywords: medication adherence, acute myocardial infarction, AMI, linked data, big data, routinely collected data, cardioprotective medications

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death globally, despite considerable advances in effective preventive treatments. It is estimated that cases of CVD have nearly doubled between 1990 and 2019, with estimates reaching 523 million prevalent cases in 2019 (Roth et al., 2020). Acute myocardial infarction (AMI) accounts for almost half of CVD-related deaths globally (Roth et al., 2017). Based on clear evidence of benefit from large-scale randomized controlled trials, all international guidelines recommend long-term secondary prevention medications for patients who have had an AMI, unless contraindicated (Guidelines for the Management of Acute Coronary Syndromes, 2006; Smith et al., 2006; National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, 2012; National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk, 2012; Roffi et al., 2016; Ibanez et al., 2017; Karmali and Lloyd-Jones, 2017). These include both lipid-lowering and blood pressure-lowering medications. Relative risk reductions in subsequent coronary events are estimated to be around 20% for every 10 mmHg reduction in blood pressure (Karmali and Lloyd-Jones, 2017) and 24% for every 1 mmol/L decline in low density lipoprotein (LDL) cholesterol (Armitage et al., 2019; Yusuf et al., 2000). Despite this compelling evidence, gaps in recommended medication use of up to 50% have been observed. (Sabate, 2003; Heeley et al., 2010; Hall et al., 2016).

Multiple factors associated with sub-optimal medication adherence in CVD have been identified. These range from patient characteristics (e.g., age, sex (Hall et al., 2016) and education (Shang et al., 2019)) to health system factors (e.g., medication cost and healthcare access (Sabate, 2003)) and provider factors (e.g., failure to prescribe, up-titrate or re-commence guideline-based medications (Heeley et al., 2010)). Psychosocial and psychological associations (e.g., patient's belief and attitudes) with adherence have also been addressed separately (Molfenter et al., 2012). There is little consistency among results (Gast and Mathes, 2019; Leslie et al., 2019) leading to difficulties identifying targets for interventions.

As research evolves from small and carefully curated data sets to large and expansive data, our understanding of the influencers of medication adherence has the opportunity to grow (Kardas et al., 2020). Large, complex and longitudinal data sources are emerging and over the last decades, more hospital administration data are becoming available for research purposes along with pharmaceutical dispensing data. Both these data sources are often developed for cost and budgeting purposes but can be used for health service research to inform clinical and pharmacoepidemiologic research (Nicholls et al., 2017). Longitudinal survey data including the Nurses' Health Studies (Belanger et al., 1978), the 45 and Up Study (45 and Up Study Collaborators, 2008), the 1970 British Cohort Study (Elliott and Shepherd, 2006) and the Millennium Cohort study (Connelly and Platt, 2014) all follow large populations over time gaining insights into participants' health and social characteristics.

Alongside increases in the availability of these rich data sources, there has been an expansion in the past 15 years of machine learning and advanced statistical methods with which to analyse such data. These advanced methods are being applied more often in a wider scientific context and in recent years these methods have been instrumental in the medication adherence paradigm (Zullig et al., 2019; Gu et al., 2021).

A more comprehensive understanding of the factors associated with adherence is needed to address treatment gaps. In this study, we use advanced statistical methods and big data to investigate adherence in people hospitalised with a first AMI. Using data from a large cohort study involving survey data, routinely collected hospital administrative and pharmaceutical dispensing data in Australia, we aimed to: 1) examine adherence over time to both a lipid-lowering medication and renin-angiotensin system (RAS) blockade post-AMI; 2) identify factors associated with adherence to both medication classes in combination; and 3) assess the strength of these associations using advanced regression methods.

METHODS

Study Context

This study uses data from the 45 and Up Study and the EXamining ouTcomEs in chroNic Disease in the 45 and Up Study (EXTEND45) Study. Details of both the 45 and Up Study (45 and Up Study Collaborators, 2008; Banks et al., 2011) and EXTEND45 (Foote et al., 2020) have been published previously. In summary, the 45 and Up Study is an Australian population-based cohort study of 267,153 men and women aged ≥45 years who were randomly sampled from the general population of New South Wales (NSW), using the Services Australia (formerly Department of Human Services) enrolment database.

Between 2006 and 2009, invited participants were asked to complete a postal questionnaire on healthy ageing and consent to ongoing linkage to their data held in routinely collected databases. The 45 and Up Study had an 18% response rate covering approximately 11% of the NSW population aged 45 years and over (45 and Up Study Collaborators, 2008) and has been shown to report near representative estimates for many of the various measures relating to risk factors estimated by the NSW health survey (Mealing et al., 2010). In the EXTEND45 Study, 45 and Up Study participants and their baseline questionnaire responses

have been linked to routinely collected administrative health datasets, outpatient laboratory results from laboratory service providers, and the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry.

Ethics Approval

The EXTEND45 Study received ethical approval from the NSW Population and Health Services Research Ethics Committee (PHSREC; study reference number HREC/13/CIPHS/69). The 45 and Up Study received ethical approval from the University of New South Wales Human Research Ethics Committee (HREC).

Data Sources

The linked data sources used within this work include 1) NSW Admitted Patient Data Collection (APDC), providing information on all public and private hospital admissions in NSW, 2) Medicare Benefits Schedule (Department of Health, Australian Government, 2021a) (MBS) database, providing information on government-subsidized medical services, 3) Pharmaceutical Benefits Scheme (Department of Health, Australian Government, 2021b) (PBS) database, an electronic dispensing record providing prescription medication claims data, 4) community laboratory services, and 5) NSW Register of Births, Deaths and Marriages (RBDM). MBS and PBS data were provided by Services Australia through a deterministic link with 45 and Up Study participants. Probabilistic linkage of all other data sources was performed by the Centre for Health Record Linkage (CHeReL) (http://www.cherel.org.au).

Study Cohort

Participants were included in the present study if they were hospitalized with their first AMI between 1st January 2006 and 1st October 2013 (hereafter referred to as the index AMI). Hospitalization records and self-reported results were used to validate an incident AMI. Further details of the selection criteria and study cohort are available in the supplementary material.

Follow-up lasted from the date of AMI hospitalization discharge until 30th June 2014 (end of available data). Participants were censored at a second AMI or death and required at least 9 months of follow up. AMI diagnoses were identified using the International Statistical Classification of Disease and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) codes (Supplementary Appendix **Supplementary Table S1**).

Covariates

Covariates included demographic, socioeconomic, lifestyle and clinical characteristics, and were derived from either self-reported information from the 45 and Up Study baseline questionnaire, PBS, MBS or laboratory data, or a combination of these. Supplementary information for covariates and Appendix **Supplementary Table S2** contains further details.

The primary exposure of interest was prior treatment with a lipid-lowering medication and/or RAS blockade (defined below), which was identified from PBS data, using a 6-months lookback interval from the index AMI (hereafter referred to as prior treatment exposure). The term "exposure" rather than "adherence" is used in the pre-AMI time period because guideline-based indications for the individual prior to the AMI cannot be ascertained in the dataset. Four mutually exclusive classes of prior treatment exposure were defined:

(1) treatment naïve, neither a lipid-lowering medication nor RAS blockade;
(2) a lipid-lowering medication but no RAS blockade;
(3) RAS blockade but no lipid-lowering medication; and
(4) both a lipid-lowering medication and RAS blockade.

Primary Outcome

The primary outcome was adherence to both lipid-lowering medications (including statins and fibrates) and RAS blockade [Angiotensin Converting Enzyme inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB)] at 12 months post-AMI. Lipid-lowering and RAS blockade treatments were selected to examine guideline-indicated medications because both medication classes in Australia require a prescription and so are systematically captured in prescription claims data. In contrast, antiplatelet medications, which are also recommended for secondary prevention, were not included because a large number are available without a prescription and so purchasing patterns using routinely collected data are unreliable (Australian Bureau of Statistics, 1011; Britt et al., 2015).

Prescriptions filled were determined using the PBS Anatomical Therapeutic Chemical (ATC) Classification Level 5 codes. (WHO Collaboating Centre for Drug Statistics Methodology, 2021). The PBS records all claims dispensed under Australia's universal public health insurance scheme that provides free or subsidized access to medications. The codes used for lipid-lowering medications were C10AA/AB/BA/BX, and for RAS blockade were C09AA/BA/CA/DA (Supplementary Appendix **Supplementary Table S3**).

Calculating Proportion of Days Covered

A participant was considered adherent to medication if they had access to the medication at least 80% of the time. Electronic dispensing data were used to identify the date of supply of a medication and the quantity supplied and hence to calculate the proportion of days covered (PDC) by these purchases.

Further details and assumptions (Arnet et al., 2016) for the calculation of PDC can be found in the supplementary material. Dual therapy adherence is addressed by requiring that participants are in receipt of both medication classes at the same time over the time interval of interest (Supplementary Appendix **Supplementary Figure S2**).

Statistical Analyses

The analysis was performed in three parts: 1) variable selection was performed to subset the large number of variables using clinical relevance and boosted regression tree (BRT) models; 2) adherence over time was observed, stratified by key variables selected in 1; and 3) multivariable regression for the primary outcome was performed on the subset of variables selected in 1.

Boosted Regression Trees for Variable Selection

The BRT (Elith et al., 2006; Elith et al., 2008) approach to variable selection allows a subset of variables to be identified according to their relative influence in explaining the variability of the outcome and frees analysis from the constraints of variable selection via p-value-based algorithms. (Derksen and Keselman, 1992; Thompson, 1995; Friedman et al., 2000; Jackson, 2008; Wasserstein and Lazar, 2016; Smith, 2018).

Adherence Over Time

The proportion of individuals who were adherent over time was also assessed, both for the overall cohort and stratified by variables found to be influential in the BRT analysis. PDC was assessed in quarterly intervals from 12 months prior to the AMI event until the end of follow up. Assessing adherence prior to the AMI allowed the impact of the AMI event on medication use to be examined. Proportions are displayed with 95% binomial confidence intervals. Longitudinal adherence to the individual medication classes was also assessed, using the previously defined lipid-lowering medication and RAS blockade ATC codes.

Multivariable Regression

Multivariable logistic regression was used to model the association of adherence with the proportion of individuals with a PDC ≥80% at the primary outcome period (between 9 and 12 months post-AMI). Variables included in the model were those informed by the BRT analysis as well as those considered to be of clinical importance based on prior literature and expert clinician input. Some highly correlated variables (such as hyperlipidemia) were removed for the primary analyses but were included in sensitivity analyses. Categorical exposure variables were modelled using linear terms and their effects illustrated using forest plots of the odds ratios and 95% confidence intervals. Age was categorized into 10-years age groups. A sensitivity analysis was performed with additional variables including seven comorbidities and highly correlated variables previously removed.

The analysis was performed using SAS version 9.4, SAS Enterprise Guide 7.1 and R version 3.6.2 (R Core Team, 2014). Cohort identification, adherence calculations and manipulations of APDC, MBS and PBS data were completed in SAS. R was used for boosted regression tree (gbm 2.1.5 (Greenwell et al., 2020)), generalized additive models (Wood, 2017) (mgcv 1.8–28), further logistic regression and statistical graphics (ggplot2 (Wickham, 2016), visreg (Breheny and Burchett, 2017)).

Patient and Public Involvement

Participant recruitment and surveying were performed by the Sax Institute as part of the 45 and Up Study. Results from this research will be disseminated to the community through The George Institute's social media platforms and website, and directly to the 45 and Up Study participants via established Sax Institute channels.

RESULTS

In total, 14,200 individuals were identified as surviving an index AMI between 2006 and 2014 and meeting the eligibility criteria (Supplementary Appendix **Supplementary Figure S2**). The mean age was 69.9 years at AMI (SD = 10.45) with 38.7% being female, and median follow-up time of almost 4 years (44.5 months IQR: 43.7 months). Key demographic, cardiovascular risk factors, comorbidities and AMI event characteristics are shown in **Table 1**.

Overall adherence increased from 18.2% (95% CI: 17.4–18.6%) at the time of the AMI to 28.0% (95% CI: 27.3–28.8%) within the first 3 months post AMI. Adherence increased to 29.5% (95% CI: 28.8–30.0%) by 12 months. After 12 months the overall adherence was maintained. By 24 months post AMI overall adherence was 28.9% (95% CI: 28.1–29.8%) (**Figure 2** grey downward vertex triangle).

Variable Selection

Of 51 characteristics included in the BRT, the 15 variables with the highest relative influence are shown in **Figure 1**. Prior treatment exposure was the most influential variable by a considerable margin, minimizing the loss function in over 70% of BRT models. All other variables had a relatively minor influence (Supplementary Appendix **Supplementary Figure S3**).

Analyses by Prior Treatment Exposure

In total 28.2% (n = 4,011) of the study cohort were treatment naïve, 26.5% (n = 3,768) had been previously exposed to lipid-lowering medication only, 12.2% (n = 1,729) to RAS blockade only, and 33.0% (n = 4,692) had been exposed to both a lipid-lowering medication and RAS blockade.

The main differences in characteristics by prior treatment exposure group relate to higher rates of pre-AMI diagnoses of hyperlipidemia and hypertension and higher primary care utilization both before and after the AMI in the groups with prior RAS blockade use and those with lipid-lowering and RAS blockade medication use compared to the other two groups (**Table 1**). Further cohort characteristics are in the supplementary material (Supplementary Appendix **Supplementary Table S4**).

The trend in post-AMI adherence differed according to pre-AMI treatment exposure (**Figure 1**). In people previously exposed to both medications, the proportion of individuals with a PDC ≥80% slowly increased in the 12 months prior to the AMI event, with 54.3% (95% CI: 52.9–55.8%) having a PDC ≥80% at the time of the event. Adherence rates then increased between the AMI and 3 months post-AMI to 68.8% (95% CI: 67.5–70.1%) and plateaued to 66.2% by 12 months (95% CI: 64.8–67.5%). The three other groups defined by prior exposure showed a moderate increase in adherence following the AMI with minimal change thereafter. (**Figure 2**).

Multivariable Analyses of Adherence

After adjustment for the most influential variables in the BRT analysis (age, income and AMI severity) and clinically informed

TABLE 1 | Cohort characteristics of people with a first AMI meeting eligibility requirements by prior exposure.

Characteristics	Treatment naïve (N = 4,011)	Prior lipid lowering exposure (N = 3,768)	Prior RAS blockade exposure (N = 1,729)	Prior lipid lowering and RAS blockade exposure (N = 4,692)	Complete eligible cohort (N = 14,200)
Demographic					
Sex (Female)	1,636 (40.8%)	1,260 (33.4%)	796 (46.0%)	1,804 (38.4%)	5,496 (38.7%)
Comorbidities					
Hypertension	1,544 (38.5%)	1,750 (46.4%)	1,476 (85.4%)	4,217 (89.9%)	8,987 (63.3%)
Hyperlipidaemia	910 (22.7%)	2,445 (64.9%)	367 (21.2%)	3,735 (79.6%)	7,457 (52.5%)
Type 2 Diabetes	354 (8.8%)	596 (15.8%)	276 (16.0%)	1,523 (32.5%)	2,749 (19.4%)
Chronic kidney disease	458 (11.4%)	442 (11.7%)	363 (21.0%)	1,031 (22.0%)	2,294 (16.2%)
Cancer	1,643 (41.0%)	1,474 (39.1%)	805 (46.6%)	2,130 (45.4%)	6,052 (42.6%)
Depression	541 (13.5%)	462 (12.3%)	198 (11.5%)	575 (12.3%)	1,776 (12.5%)
Stroke	145 (3.6%)	154 (4.1%)	92 (5.3%)	381 (8.1%)	772 (5.4%)
Characteristics of AMI					
Mean age at AMI (SD)	67.5 (11.73)	67.1 (9.94)	73.6 (9.49)	72.8 (8.71)	69.9 (10.45)
Median length of stay (Q1; Q3)	2.0 (1.0; 6.0)	1.0 (1.0; 5.0)	3.0 (1.0; 8.0)	2.0 (1.0; 7.0)	2.0 (1.0; 6.0)
STEMI/Non-STEMI					
STEMI	380 (9.5%)	236 (6.3%)	144 (8.3%)	315 (6.7%)	1,075 (7.6%)
Non-STEMI	832 (21.0%)	567 (15.3%)	404 (23.7%)	918 (20.1%)	2,721 (19.5%)
Unspecified	2,799 (69.8%)	2,965 (78.7%)	1,181 (68.3%)	3,459 (73.7%)	10,404 (73.3%)
Complications					
Cardiac Arrest	26 (0.6%)	19 (0.5%)	12 (0.7%)	29 (0.6%)	86 (0.6%)
Cardiogenic Shock	11 (0.3%)	6 (0.2%)	8 (0.5%)	18 (0.4%)	43 (0.3%)
Management strategy					
Coronary angiogram only	469 (11.7%)	453 (12.0%)	189 (10.9%)	605 (12.9%)	1,716 (12.1%)
Percutaneous coronary intervention	2,930 (73.0%)	3,004 (79.7%)	1,205 (69.7%)	3,445 (73.4%)	10,584 (74.5%)
Coronary artery bypass grafting	135 (3.4%)	271 (7.2%)	74 (4.3%)	388 (8.3%)	868 (6.1%)
Primary Care Engagement Prior to AMI					
Primary care visits within 1 month[a] (mean (SD))	0.9 (1.22)	1.0 (1.18)	1.2 (1.35)	1.2 (1.36)	1.1 (1.28)
Primary care visits between 2 and 6 months[b] (mean (SD))	4.1 (4.00)	4.9 (3.97)	6.5 (5.15)	6.4 (4.56)	5.4 (4.46)
Post-AMI					
Primary care visits within 1 month[a] (mean (SD))	1.4 (1.58)	1.5 (1.37)	1.9 (1.64)	1.8 (1.59)	1.6 (1.55)
Primary care visits between 2 and 6 months[b] (mean (SD))	5.5 (5.32)	5.9 (4.77)	8.0 (5.89)	7.8 (5.58)	6.7 (5.46)

[a]*GP, visits within 28 days of AMI.*
[b]*GP, visits between 29 and 180 days of AMI.*

variables (sex and education level), post-AMI medication adherence was clearly different in groups defined by prior treatment exposure (**Figure 3**).

Compared to treatment naïve, those who had been dispensed both medication classes in the 12 months prior to their AMI were over 9 times more likely (RR = 9.3, 95% CI: 8.54–10.13) to be adherent to both medication classes following the index AMI with an odd ratio of 21.73 (95% CI: 18.47 to 25.56, n = 4,692). Those exposed to only lipid-lowering medication were 33% more likely to be adherent (OR 1.33, 95% CI: 1.09 to 1.62, n = 3,768) and those recently treated with only RAS blockade had a 3-fold increase (OR 3.26, 95% CI: 2.68 to 3.96, n = 1729) than treatment naïve. Prior treatment exposure explained 31.3% of the variance in adherence associated with the adherence in the outcome interval in the overall cohort ($R2_{adjusted}$ = 0.353).

Results were similar in a sensitivity analysis performed on an expanded variable set which included prior treatment exposure, age, sex, income, education level, AMI severity and seven comorbidities. In these analyses, the odds ratio for people previously dispensed both medications compared with no prior treatment exposure was 14.49 (95% CI: 12.14 to 17.29, n = 4,692) (Supplementary Appendix **Supplementary Figure S4**).

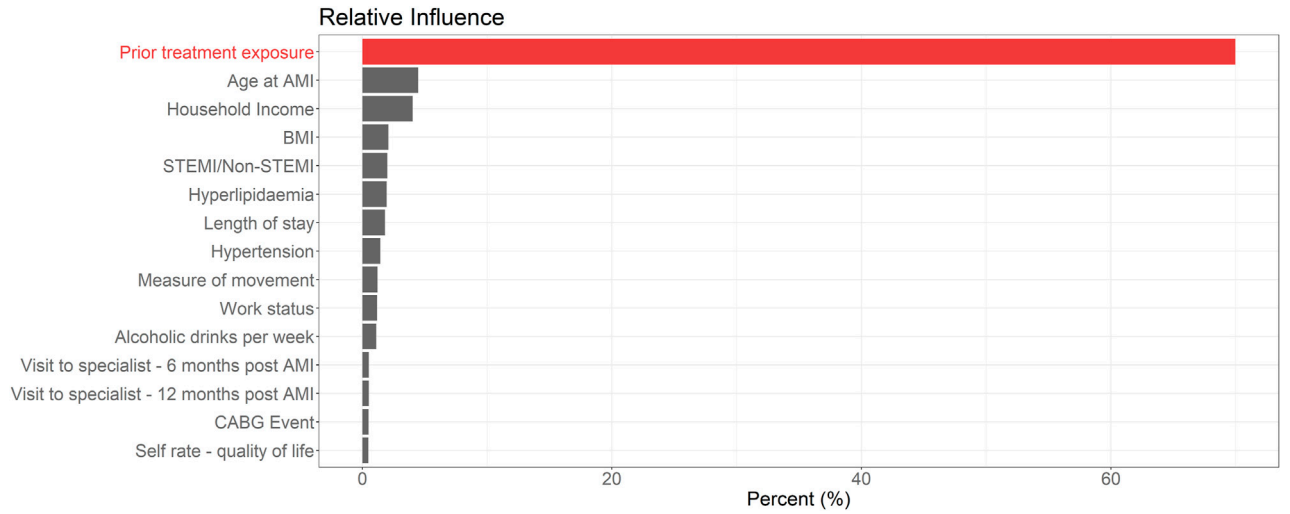


FIGURE 1 | Top 15 variables when ranked *via* relative influence from boosted regression tree models for medication adherence 12 months post AMI.

DISCUSSION

In this cohort study of 14,200 people hospitalized for a first AMI event, less than 30% of individuals were consistently adherent to both guideline-based medication classes at 12 months post-AMI. Adherence increased substantially in the 3-months interval following the AMI compared with utilization of the same medications prior to the AMI. However, the occurrence of the AMI itself only explained a minority of the post-infarct cardioprotective medication use. Prior medication use was the factor most strongly associated with adherence post-AMI. Nearly two-thirds of people taking these medicines pre-AMI were adherent at 12 months, and were around 9 times more likely to be adherent compared with those who had been dispensed neither classes prior to the AMI. This association was far stronger than other commonly-cited associations in the literature, including age and AMI event severity (Sabate, 2003; Heeley et al., 2010; Molfenter et al., 2012; Laba et al., 2013; Hall et al., 2016; Shang et al., 2019).

Implications for Practice and Policy

The findings suggest that prescribing clinicians need robust systems in place to systematically determine prior medication exposure when assessing risks of non-adherence post-AMI. Intensified efforts are needed for all patients along with strategies that address both provider and patient barriers to adherence (Sabate, 2003; Kolandaivelu et al., 2014; Abbass et al., 2017; Burnier and Egan, 2019; Gast and Mathes, 2019). This applies to all patients but particularly for people with no prior use of lipid-lowering and RAS blockade medication. Only 7.1% of this group were optimally adherent to both therapies 12 months post-AMI. Prior treatment exposure is best identified via continuity of patient care. Policies around management plans supporting continuous relationships between patient and clinician should be encouraged, especially for patients with chronic or complex conditions.

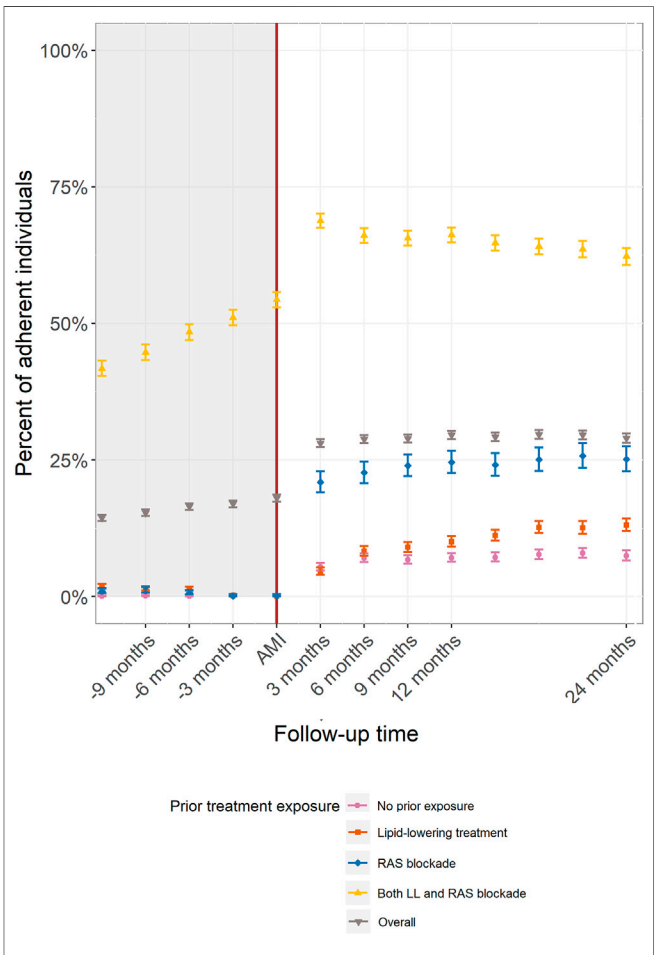


FIGURE 2 | Adherence to both lipid-lowering and RAS blockade treatments by pre-AMI treatment exposure.

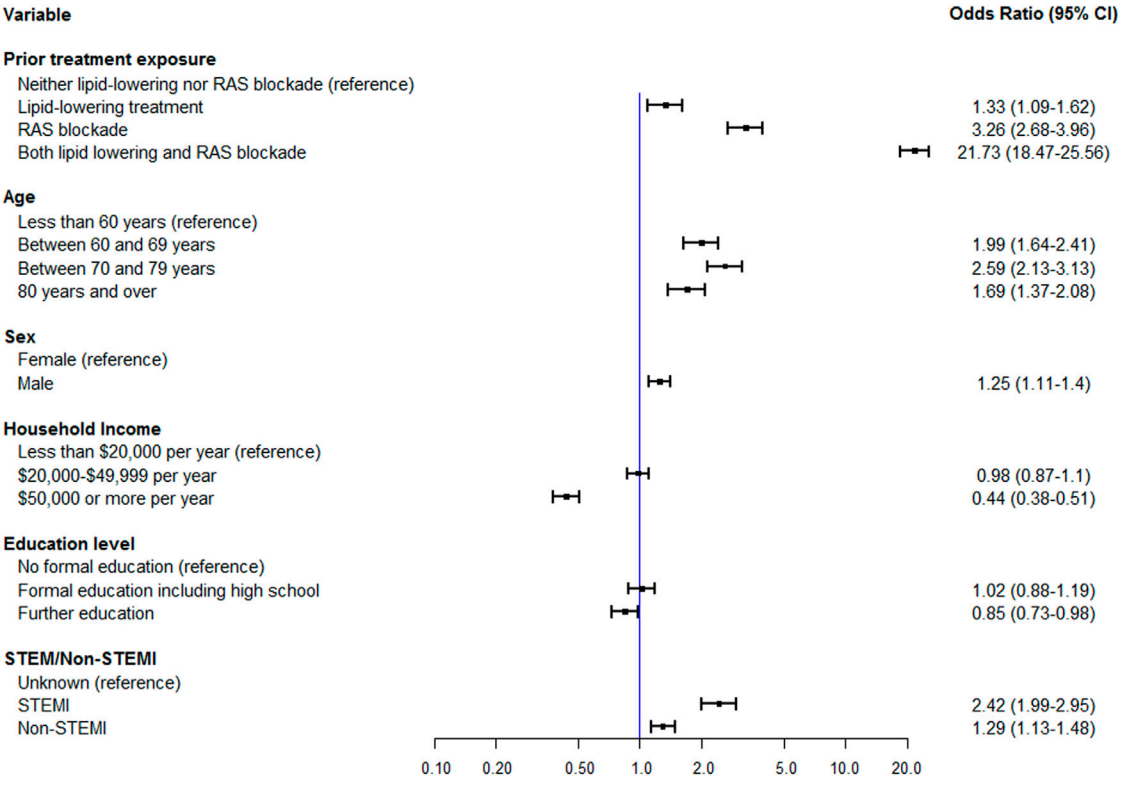


FIGURE 3 | Multivariable logistic regression of adherence at 12 months post AMI by prior treatment exposure including age, sex, income, education level and STEMI/Non-STEMI status.

Discharge counselling is an important component to patient health post-AMI. Our study shows that the first 3 months post-AMI have been shown to be crucial to developing good adherence. Guidelines exist around medication counselling that include patient education, medication management and disease management (Cai et al., 2013; Mathews et al., 2015a). The findings from this study indicate that the primary catalyst to adherence post event is not the initial AMI but previous medication exposure. Therefore, prior exposure needs to be a key consideration in the discharge medication counselling performed by the in-hospital pharmacist.

Integration of often fragmented health systems (World Health Organization, 2015) can support a wholistic and patient centered model of care which is an important component for medication adherence. New South Wales, Australian, has implemented a state-wide integrated care strategy. This strategy is focused on coordinating connection and communication between health care providers in the community and those in the hospital setting (NSW Health, 2020).

Community pharmacists can also play a critical role in enhancing support for patients at high risk of non-adherence. Although medication adherence interventions have had limited impact (Nieuwlaat et al., 2014), interventions have showed some success when administered through these services (Torres-Robles et al., 2021). In an environment of limited time and resources, targeting patients with the greatest need is key to making impacts in overall community adherence (Zullig et al., 2019). Prior treatment exposure is a tangible patient characteristic that a pharmacist can identify without a complex assessment. It is a scalable method to identify potential candidates for services that may help medication adherence in the initial months after an AMI including medication counselling, adherence support and follow-up (Jackevicius et al., 2008). Voluntary medication reviews by a pharmacist could be made available. Prior medication use should be a standard consideration in medication discussions.

The Findings in the Context of Previous Evidence

The plateau in adherence overall and for all pre-event exposure groups at 12 months post-AMI differ from some (Jackevicius et al., 2002; Mathews et al., 2015b) but not all (Harrison et al., 2018) previous studies, which have mostly found adherence to decline over time. Differences between our study and previous reports, including adherence methodology, data sources and settings (comprehensive government-subsidized pharmaceutical benefits scheme vs. insurance claim data), making direct comparisons difficult.

The reason why prior medication utilization is associated with better post-infarct utilization cannot be determined from these results and may be mediated by multiple health service, practitioner and patient characteristics. Taking lifelong treatments is a complex adaptive process and it is possible patients who are already taking at least some of the recommended medication may not need to make

as major changes in their medication-taking behavior post-AMI compared with those who were treatment naïve pre-event (Molfenter et al., 2012; Brown et al., 2016; Kini and Ho, 2018; Armitage et al., 2019).

It is reassuring that studies using single class adherence to lipid-lowering and RAS blockade medications from the United States (Akincigil et al., 2008) and Canada (Rasmussen et al., 2007) report higher levels of monotherapy adherence. Other single class studies using large data sources and advanced statistical techniques have also identified prior medication use as an important component to predict medication adherence when only a single class of medications is assessed (Zullig et al., 2019).

People who were exposed to both medications pre-AMI were older and have a greater burden of comorbidities, mainly hypertension and hyperlipidemia. The higher primary care utilization rates post-AMI observed in those on prior RAS blockade or simultaneous lipid-lowering medications and RAS blockade treatments may mean these two groups have a greater frequency of interactions with health care providers allowing more opportunity for renewal of prescriptions and appropriate adjustments to medication. Our study confirmed early reports that age (Chang et al., 2015) and AMI severity (Ge et al., 2019) are associated with treatment adherence. Similar to previous studies we found a non-linear associations of age with adherence in people aged 70 to 79-years-old higher than for younger or older age-groups (Chang et al., 2015).

We also observed that higher income was associated with lower adherence rates, when adjusted for education, age and AMI severity. There are varied associations between wealth and adherence in literature (Chernew et al., 2008; Abbass et al., 2017; González López-Valcárcel et al., 2017) and this may partly reflect variation in health system policies. As part of Australia's universal health care coverage scheme, medications are heavily subsidized for low income individuals/households (e.g., a two or more person household with an income less than $50,000) and may contribute to the complex associations when assessing the relationship between wealth and adherence. Furthering the complex impact of income are financial threshold safety nets that are available to high health system users in the Australian community, for example people taking multiple medications or those with a high number of comorbidities. Eligible patients receive prescriptions and some health care services at a reduced cost. This scheme further removes cost barriers to medication and primary care visits for patients with high utilization patterns and multiple health needs.

Strengths and Limitations of the Study

This study has many strengths from both the methodology and the data sets. BRT models identify key variables even in the presence of high correlation. In such cases the most informative variable will result in a higher relative influence score. The 45 and Up Study is large with over 250,000 participants with a range of variables including both survey and routinely collected data. Large and extensive data sets spanning such a diverse array of personal factors are uncommon. The adherence method used in this study is objective and comprehensive as it used dispensing data from the nationwide pharmacy network.

The use of national prescribing claims data enables complete follow-up of participants and is not prone to recall bias from self-report (Sabate, 2003; Garber et al., 2004). Through the utilization of medication dispensing data to identify exposure to medications prior to the AMI, associations with adherence following the AMI were able to be identified. Longitudinal studies of medication dispensing before and after a major event are not common.

A limitation is the inability to identify whether treatment gaps are due to non-prescribing by the care provider, or non-prescription filling or non-taking by the patient. In a recent study of general practice prescribing patterns in NSW, less than 60% of patients with an established diagnoses of cardiovascular disease diagnosis had a current prescription for guideline-recommended medications (Hespe et al., 2020). Another study limitation is that we lacked information on contraindications to the two medications. However, the highest rates of major contraindications to these medications is around 1.5–5% (mainly related to RAS blockade medications) (Bays, 2006; Caldeira et al., 2012; Clase et al., 2020) and therefore contraindications are unlikely to explain the overall low adherence rates observed in this study (Keen et al., 2014; Laufs et al., 2015; Ward et al., 2019). The data used in this study extends from 2006 to 2014. Nevertheless, the nature of medication adherence and the influencers of behavior are unlikely to have changed substantially in the 8 years since 2014. Our conclusions therefore remain applicable. Guideline-recommended cardioprotective medications were adjusted to reflect best practice at the time the data was collected. Finally, the results relate to people who have experience an initial AMI and may not be generalizable to those experiencing multiple events.

Large and constantly evolving data sources offer ready opportunities for further research. In the context of this study, examining the influence of poly pills (Roshandel et al., 2019) on medication adherence could highlight an interesting influence with both the ease of one pill and the mitigated side effect from the dual treatment. Further, the scope of personal characteristics can be further examined with greater interrogation into hereditary conditions and comorbidities such as post AMI mental health and how this impacts medication adherence (Thombs et al., 2006). As follow up progresses data will yield a greater number of subsequent cardiovascular events. Adherence in relation to subsequent AMIs could also be examined.

CONCLUSION

Sub-optimal adherence to best practice care guidelines is a complex and intractable challenge in many areas of health care. Although a robust evidence base for secondary prevention of cardiovascular disease events for people who have had an AMI exists, a large proportion of people are not receiving the benefits of pharmacotherapy support. This adherence gaps contributes to avoidable personal burden and societal costs. Overall the optimal use of life-saving, low cost therapies after an AMI is low. These low adherence rates indicate that systematic appraisal of the risk of non-adherence in the immediate post-AMI period represents a potential opportunity to improve outcomes for individuals. Particular attention should be paid to a patient's prior cardiovascular treatments pre-AMI. Results from this

large data analysis show that prior treatment is a key influence to post AMI medication adherence. Of crucial concern are people who have had no prior experience with taking the recommended medications.

DATA AVAILABILITY STATEMENT

The data analyzed in this study was obtained from https://www.saxinstitute.org.au/our-work/45-up-study/, the following licenses/restrictions apply: institutional restrictions. Requests to access these datasets should be directed to the Sax Institute, 45andUp.research@saxinstitute.org.au.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The EXTEND45 Study received ethical approval from the NSW Population and Health Services Research Ethics Committee (PHSREC; study reference number HREC/13/CIPHS/69). The 45 and Up Study received ethical approval from the University of New South Wales Human Research Ethics Committee (HREC). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualisation: AC, CH, LS, MJa *Data Curation:* AC, KR, *Formal Analysis:* AC *Funding acquisition:* MJ, CC, AC, DS, MJu, CPollock, DPeiris, *Investigation:* AC, CH, LS, *Methodology:* AC, KR, CH, LS, *Project administration:* CH, *Supervision:* MJa, DP, *Validation:* CH, KR, *Visualisation:* AC, *Writing original draft:* AC, CH, LS, DP, MJa, *Writing review and editing:* AC, CH, LS, KR, DP, MJa, CC, AC, DS, MJu, CP, TL.

FUNDING

This work was funded by a NSW Cardiovascular Research Network Development Project Grant from the National Heart Foundation of Australia (award no. 100720). The broader EXTEND45 Study is in part funded through peer-reviewed, unconditional grants, including a seeding GENESIS grant supported by Roche Products Pty Ltd. (grant no. FR-MIR-0095) and a Rebecca L Cooper Grant (grant no. REB002). In addition, the EXTEND45 Study has received unconditional research grants from Eli Lilly (Australia) Pty Ltd. (grant no. PO4100294024), Merck Sharp and Dohme (Australia) Pty Ltd. (grant no. MSD_EXTEND45), and Amgen (Australia) Pty Ltd. (grant no. Amgen01). TL is currently supported by a NHMRC Early Career Fellowship (APP1141392) and National Heart Foundation Postdoctoral Fellowship (award ID 101956) CC is supported by a NHMRC Investigator grant. AC's cardiovascular medication adherence research is supported by CVH CAG Seed Grant 2021.

ACKNOWLEDGMENTS

This research was completed using data collected through the 45 and Up Study (www.saxinstitute.org.au). The 45 and Up Study is managed by the Sax Institute in collaboration with major partner Cancer Council NSW; and partners: the Heart Foundation; NSW Ministry of Health; NSW Department of Communities and Justice; and Australian Red Cross Lifeblood. We thank the many thousands of people participating in the 45 and Up Study. In addition, the authors thank Services Australia (formerly Department of Human Services) for their supply of MBS and PBS data and the private pathology companies who have contributed their data to this study. Data linkage was performed by the Sax Institute and the Centre for Health Record Linkage (CHeReL) (https://www.cherel.org.au). Acknowledgment of the Members of the EXTEND45 Steering Committee. MJa, CH, MJu, KR, AC, CP, CKC, EC, Celine Foote, Martin Gallagher, John Knight, Martin McNamara, Bette Liu, TL, DP, DS, Roger Wilson, Germaine Wong, Sophia Zoungas.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.834898/full#supplementary-material

REFERENCES

45 and Up Study CollaboratorsBanks, E., Redman, S., Jorm, L., Armstrong, B., Bauman, A., et al. (2008). Cohort Profile: The 45 and Up Study. *Int. J. Epidemiol.* 37 (5), 941–947. doi:10.1093/ije/dym184

Abbass, I., Revere, L., Mitchell, J., and Appari, A. (2017). Medication Nonadherence: The Role of Cost, Community, and Individual Factors. *Health Serv. Res.* 52 (4), 1511–1533. doi:10.1111/1475-6773.12547

Akincigil, A., Bowblis, J. R., Levin, C., Jan, S., Patel, M., and Crystal, S. (2008). Long-term Adherence to Evidence Based Secondary Prevention Therapies after Acute Myocardial Infarction. *J. Gen. Intern. Med.* 23 (2), 115–121. doi:10.1007/s11606-007-0351-9

Armitage, J., Baigent, C., Barnes, E., Betteridge, D. J., Blackwell, L., Blazing, M., et al. (2019). Efficacy and Safety of Statin Therapy in Older People: a Meta-Analysis of Individual Participant Data from 28 Randomised Controlled Trials. *Lancet* 393 (10170), 407–415. doi:10.1016/S0140-6736(18)31942-1

Arnet, I., Kooij, M. J., Messerli, M., Hersberger, K. E., Heerdink, E. R., and Bouvy, M. (2016). Proposal of Standardization to Assess Adherence with Medication Records: Methodology Matters. *Ann. Pharmacother.* 50 (5), 360–368. doi:10.1177/1060028016634106

Australian Bureau of Statistics Remoteness Structure. Available from: https://www.abs.gov.au/websitedbs/d3310114.nsf/home/remoteness+structure.

Banks, E., Jorm, L., and Wutzke, S. (2011). The 45 and up Study: Fostering Population Health Research in NSW. *N. S W Public Health Bull.* 22 (1-2), 15–16. doi:10.1071/NB10063

Bays, H. (2006). Statin Safety: an Overview and Assessment of the Data--2005. *Am. J. Cardiol.* 97 (8A), 6C–26C. doi:10.1016/j.amjcard.2005.12.006

Belanger, C. F., Hennekens, C. H., Rosner, B., and Speizer, F. E. (1978). The Nurses' Health Study. *Am. J. Nurs.* 78 (6), 1039–1040. doi:10.2307/3462013

Breheny, P., and Burchett, W. (2017). Visualization of Regression Models Using Visreg. *R. J.* 9 (2), 56–71. doi:10.32614/rj-2017-046

Britt, H., Miller, G. C., Henderson, J., Bayram, C., Harrison, C., Valenti, L., et al. (2015). *General Practice Activity in Australia 2014–15*. General Practice Series No. 38. Sydney: Sydney University Press. Available at: purl.library.usyd.edu.au/sup/9781743324523.

Brown, M. T., Bussell, J., Dutta, S., Davis, K., Strong, S., and Mathew, S. (2016). Medication Adherence: Truth and Consequences. *American J. Med. Sci.* 351 (4), 387–399. doi:10.1016/j.amjms.2016.01.010

Burnier, M., and Egan, B. M. (2019). Adherence in Hypertension. *Circ. Res.* 124 (7), 1124–1140. doi:10.1161/CIRCRESAHA.118.313220

Cai, H., Dai, H., Hu, Y., Yan, X., and Xu, H. (2013). Pharmacist Care and the Management of Coronary Heart Disease: a Systematic Review of Randomized Controlled Trials. *BMC Health Serv. Res.* 13 (1), 461. doi:10.1186/1472-6963-13-461

Caldeira, D., David, C., and Sampaio, C. (2012). Tolerability of Angiotensin-Receptor Blockers in Patients with Intolerance to Angiotensin-Converting Enzyme Inhibitors: a Systematic Review and Meta-Analysis. *Am. J. Cardiovasc. Drugs* 12 (4), 263–277. doi:10.1007/BF03261835

Chang, T. E., Ritchey, M. D., Park, S., Chang, A., Odom, E. C., Durthaler, J., et al. (2015). National Rates of Nonadherence to Antihypertensive Medications Among Insured Adults with Hypertension, 2015. *Hypertension* 74 (746), 1324–1332. doi:10.1161/HYPERTENSIONAHA.119.13616

Chernew, M. E., Shah, M. R., Wegh, A., Rosenberg, S. N., Juster, I. A., Rosen, A. B., et al. (2008). Impact of Decreasing Copayments on Medication Adherence within A Disease Management Environment. *Health Aff. (Millwood)* 27 (1), 103–112. doi:10.1377/hlthaff.27.1.103

Clase, C. M., Carrero, J. J., Ellison, D. H., Grams, M. E., Hemmelgarn, B. R., Jardine, M. J., et al. (2020). Potassium Homeostasis and Management of Dyskalemia in Kidney Diseases: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 97 (1), 42–61. doi:10.1016/j.kint.2019.09.018

Connelly, R., and Platt, L. (2014). Cohort Profile: UK Millennium Cohort Study (MCS). *Int. J. Epidemiol.* 43 (6), 1719–1725. doi:10.1093/ije/dyu001

Department of Health, Australian Government (2021a). MBS Online: Medicare Benefits Schedule. Canberra: ACT: Commonwealth of Australia. Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home. [Homepage on the Internet].

Department of Health, Australian Government (2021b). PBS Online: Pharmaceutical Benefits Schedule. Canberra: ACT: Commonwealth of Australia. Available from: http://www.health.gov.au/pbs. [Homepage on the Internet].

Derksen, S., and Keselman, H. J. (1992). Backward, Forward and Stepwise Automated Subset Selection Algorithms: Frequency of Obtaining Authentic and Noise Variables. *Br. J. Math. Stat. Psychol.* 45 (2), 265–282. doi:10.1111/j.2044-8317.1992.tb00992.x

Elith, J., Graham, H., Anderson, R., Dudík, M., Ferrier, S., Guisan, A., et al. (2006). Novel Methods Improve Prediction of Species' Distributions from Occurrence Data. *Ecography* 29 (2), 129–151.

Elith, J., Leathwick, J. R., and Hastie, T. (2008). A Working Guide to Boosted Regression Trees. *J. Anim. Ecol.* 77 (4), 802–813. doi:10.1111/j.1365-2656.2008.01390.x

Elliott, J., and Shepherd, P. (2006). Cohort Profile: 1970 British Birth Cohort (BCS70). *Int. J. Epidemiol.* 35 (4), 836–843. doi:10.1093/ije/dyl174

Foote, C., Hockham, C., Sukkar, L., Campain, A., Kang, A., Young, T., et al. (2020). EXamining ouTcomEs in chroNic Disease in the 45 and up Study (The EXTEND45 Study): Protocol for an Australian Linked Cohort Study. *JMIR Res. Protoc.* 9 (4), e15646. doi:10.2196/15646

Friedman, J., Hastie, T., and Tibshirani, R. (2000). Additive Logistic Regression: A Statistical View of Boosting. *Ann. Stat.* 28, 337–407. doi:10.1214/aos/1016218223

Garber, M. C., Nau, D. P., Erickson, S. R., Aikens, J. E., and Lawrence, J. B. (2004). The Concordance of Self-Report with Other Measures of Medication Adherence: a Summary of the Literature. *Med. Care* 42 (7), 649–652. doi:10.1097/01.mlr.0000129496.05898.02

Gast, A., and Mathes, T. (2019). Medication Adherence Influencing Factors-An (Updated) Overview of Systematic Reviews. *Syst. Rev.* 8 (1), 112. doi:10.1186/s13643-019-1014-8

Ge, Z., Baber, U., Claessen, B. E., Farhan, S., Chandrasekhar, J., Li, S. X., et al. (2019). The Prevalence, Predictors and Outcomes of Guideline-Directed Medical Therapy in Patients with Acute Myocardial Infarction Undergoing PCI, an Analysis from the PROMETHEUS Registry. *Catheter Cardiovasc. Interv.* 93 (3), E112–E9. doi:10.1002/ccd.27860

González López-Valcárcel, B., Librero, J., García-Sempere, A., Peña, L. M., Bauer, S., Puig-Junoy, J., et al. (2017). Effect of Cost Sharing on Adherence to Evidence-Based Medications in Patients with Acute Coronary Syndrome. *Heart* 103 (14), 1082–1088. doi:10.1136/heartjnl-2016-310610

Greenwell, B., Boehmke, B., and Cunningham, J., GBM Developers. Gbm: Generalized Boosted Regression Models. 2020.

Gu, Y., Zalkikar, A., Liu, M., Kelly, L., Hall, A., Daly, K., et al. (2021). Predicting Medication Adherence Using Ensemble Learning and Deep Learning Models with Large Scale Healthcare Data. *Sci. Rep.* 11 (1), 18961. doi:10.1038/s41598-021-98387-w

Guidelines for the Management of Acute Coronary Syndromes (2006). *Medical Journal of Australia* 184, S1–S32. doi:10.5694/j.1326-5377.2006.tb00304.x

Hall, A. E., Paul, C., Bryant, J., Lynagh, M. C., Rowlings, P., Enjeti, A., et al. (2016). To Adhere or Not to Adhere: Rates and Reasons of Medication Adherence in Hematological Cancer Patients. *Crit. Rev. Oncol. Hematol.* 97, 247–262. doi:10.1016/j.critrevonc.2015.08.025

Harrison, T. N., Scott, R. D., Cheetham, T. C., Chang, S. C., Hsu, J. Y., Wei, R., et al. (2018). Trends in Statin Use 2009-2015 in a Large Integrated Health System: Pre- and Post-2013 ACC/AHA Guideline on Treatment of Blood Cholesterol. *Cardiovasc. Drugs Ther.* 32 (4), 397–404. doi:10.1007/s10557-018-6810-1

Heeley, E. L., Peiris, D. P., Patel, A. A., Cass, A., Weekes, A., Morgan, C., et al. (2010). Cardiovascular Risk Perception and Evidence-Ppractice Gaps in Australian General Practice (The AusHEART Study). *Med. J. Aust.* 192, 254–259. doi:10.5694/j.1326-5377.2010.tb03502.x

Hespe, C., Campain, A., Webster, R., Patel, A., Rychetnik, L., Harris, M., et al. (2020). Implementing Cardiovascular Disease Preventive Care Guidelines in General Practice: an Opportunity Missed. *Med. J. Aust.* doi:10.5694/mja2.50756

Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H., et al. (2017). 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* 39 (2), 119–177. doi:10.1093/eurheartj/ehx393

Jackevicius, C. A., Li, P., and Tu, J. V. (2008). Prevalence, Predictors, and Outcomes of Primary Nonadherence after Acute Myocardial Infarction. *Circulation* 117 (8), 1028–1036. doi:10.1161/CIRCULATIONAHA.107.706820

Jackevicius, C. A., Mamdani, M., and Tu, J. V. (2002). Adherence with Statin Therapy in Elderly Patients with and without Acute Coronary Syndromes. *JAMA* 288 (4), 462–467. doi:10.1001/jama.288.4.462

Jackson, C. H. (2008). Displaying Uncertainty with Shading. *The American Statistician* 62 (4), 340–347. doi:10.1198/000313008x370843

Kardas, P., Aguilar-Palacio, I., Almada, M., Cahir, C., Costa, E., Giardini, A., et al. (2020). The Need to Develop Standard Measures of Patient Adherence for Big Data: Viewpoint. *J. Med. Internet Res.* 22 (8), e18150. doi:10.2196/18150

Karmali, K. N., and Lloyd-Jones, D. M. (2017). Global Risk Assessment to Guide Blood Pressure Management in Cardiovascular Disease Prevention. *Hypertension* 69 (3), e2–e9. doi:10.1161/HYPERTENSIONAHA.116.08249

Keen, H. I., Krishnarajah, J., Bates, T. R., and Watts, G. F. (2014). Statin Myopathy: the Fly in the Ointment for the Prevention of Cardiovascular Disease in the 21st century? *Expert Opin. Drug Saf.* 13 (9), 1227–1239. doi:10.1517/14740338.2014.937422

Kini, V., and Ho, P. M. (2018). Interventions to Improve Medication Adherence: A Review. *JAMA* 320 (23), 2461–2473. doi:10.1001/jama.2018.19271

Kolandaivelu, K., Leiden, B. B., O'Gara, P. T., and Bhatt, D. L. (2014). Non-adherence to Cardiovascular Medications. *Eur. Heart J.* 35 (46), 3267–3276. doi:10.1093/eurheartj/ehu364

Laba, T. L., Bleasel, J., Brien, J. A., Cass, A., Howard, K., Peiris, D., et al. (2013). Strategies to Improve Adherence to Medications for Cardiovascular Diseases in Socioeconomically Disadvantaged Populations: A Systematic Review. *Int. J. Cardiol.* 167, 2430–2440. doi:10.1016/j.ijcard.2013.01.049

Laufs, U., Scharnagl, H., and März, W. (2015). Statin Intolerance. *Curr. Opin. Lipidol.* 26, 492–501. doi:10.1097/MOL.0000000000000236

Leslie, K. H., McCowan, C., and Pell, J. P. (2019). Adherence to Cardiovascular Medication: a Review of Systematic Reviews. *J. Public Health (Oxf)* 41 (1), e84–e94. doi:10.1093/pubmed/fdy088

Mathews, R., Peterson, E. D., Honeycutt, E., Chin, C. T., Effron, M. B., Zettler, M., et al. (2015). Early Medication Nonadherence after Acute Myocardial Infarction: Insights into Actionable Opportunities from the TReatment with ADP Receptor iNhibitorS: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) Study. *Circ. Cardiovasc. Qual. Outcomes* 8 (4), 347–356. doi:10.1161/CIRCOUTCOMES.114.001223

Mathews, R., Wang, T. Y., Honeycutt, E., Henry, T. D., Zettler, M., Chang, M., et al. (2015). Persistence with Secondary Prevention Medications after Acute Myocardial Infarction: Insights from the TRANSLATE-ACS Study. *Am. Heart J.* 170 (1), 62–69. doi:10.1016/j.ahj.2015.03.019

Mealing, N. M., Banks, E., Jorm, L. R., Steel, D. G., Clements, M. S., and Rogers, K. D. (2010). Investigation of Relative Risk Estimates from Studies of the Same Population with Contrasting Response Rates and Designs. *BMC Med. Res. Methodol.* 10, 26. doi:10.1186/1471-2288-10-26

Molfenter, T. D., Bhattacharya, A., and Gustafson, D. H. (2012). The Roles of Past Behavior and Health Beliefs in Predicting Medication Adherence to a Statin Regimen. *Patient Prefer Adherence* 6, 643–651. doi:10.2147/PPA.S34711

National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (2012). *Reducing Risk in Heart Disease: An Expert Guide to Clinical Practice for Secondary Prevention of Coronary Heart Disease*. Melbourne: National Heart Foundation of Australia.

National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. 2012.

Nicholls, S. G., Langan, S. M., and Benchimol, E. I. (2017). Routinely Collected Data: the Importance of High-Quality Diagnostic Coding to Research. *CMAJ* 189 (33), E1054–E5. doi:10.1503/cmaj.170807

Nieuwlaat, R., Wilczynski, N., Navarro, T., Hobson, N., Jeffery, R., Keepanasseril, A., et al. (2014). Interventions for Enhancing Medication Adherence. *Cochrane Database Syst. Rev.*, CD000011. doi:10.1002/14651858.CD000011.pub4

NSW Health (2020). *What is Integrated Care? Updated 21 2020* Available from: https://www.health.nsw.gov.au/integratedcare/Pages/what-is-integrated-care.aspx.

Rasmussen, J. N., Chong, A., and Alter, D. A. (2007). Relationship between Adherence to Evidence-Based Pharmacotherapy and Long-Term Mortality after Acute Myocardial Infarction. *Jama* 297 (2), 177–186. doi:10.1001/jama.297.2.177

R Core Team (2020). *R: A language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. https://www.R-project.org/.

Roffi, M., Patrono, C., Collet, J. P., Mueller, C., Valgimigli, M., Andreotti, F., et al. (2016). 2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* 37 (3), 267–315. doi:10.1093/eurheartj/ehv320

Roshandel, G., Khoshnia, M., Poustchi, H., Hemming, K., Kamangar, F., Gharavi, A., et al. (2019). Effectiveness of Polypill for Primary and Secondary Prevention of Cardiovascular Diseases (PolyIran): a Pragmatic, Cluster-Randomised Trial. *Lancet* 394 (10199), 672–683. doi:10.1016/S0140-6736(19)31791-X

Roth, G. A., Johnson, C., Abajobir, A., Abd-Allah, F., Abera, S. F., Abyu, G., et al. (2017). Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J. Am. Coll. Cardiol.* 70 (1), 1–25. doi:10.1016/j.jacc.2017.04.052

Roth, G. A., Mensah, G. A., Johnson, C. O., Addolorato, G., Ammirati, E., Baddour, L. M., et al. (2020). Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update from the GBD 2019 Study. *J. Am. Coll. Cardiol.* 76 (25), 2982–3021. doi:10.1016/j.jacc.2020.11.010

Sabate, E. E., *Adherence to Long-Term Therapies: Evidence for Action*. 2003/12/12ed. Geneva, Switzerland:: World Health Organization; 2003

Shang, P., Liu, G. G., Zheng, X., Ho, P. M., Hu, S., Li, J., et al. (2019). Association between Medication Adherence and 1-Year Major Cardiovascular Adverse Events after Acute Myocardial Infarction in China. *J. Am. Heart Assoc.* 8, e011793. doi:10.1161/JAHA.118.011793

Smith, G. (2018). Step Away from Stepwise. *J. Big Data* 5 (1), 32. doi:10.1186/s40537-018-0143-6

Smith, S. C., Allen, J., Blair, S. N., Bonow, R. O., Brass, L. M., Fonarow, G. C., et al. (2006). AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2006 Update: Endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 113 (19), 2363–2372. doi:10.1161/CIRCULATIONAHA.106.174516

Thombs, B. D., Bass, E. B., Ford, D. E., Stewart, K. J., Tsilidis, K. K., Patel, U., et al. (2006). Prevalence of Depression in Survivors of Acute Myocardial Infarction. *J. Gen. Intern. Med.* 21 (1), 30–38. doi:10.1111/j.1525-1497.2005.00269.x

Thompson, B. (1995). Stepwise Regression and Stepwise Discriminant Analysis Need Not Apply Here: A Guidelines Editorial. *Educ. Psychol. Meas.* 55 (4), 525–534. doi:10.1177/0013164495055004001

Torres-Robles, A., Benrimoj, S. I., Gastelurrutia, M. A., Martinez-Martinez, F., Peiro, T., Perez-Escamilla, B., et al. (2021). Effectiveness of a Medication Adherence Management Intervention in a Community Pharmacy Setting: a Cluster Randomised Controlled Trial. *BMJ Qual. Saf.*, 2020–011671. doi:10.1136/bmjqs-2020-011671:bmjqs-

Ward, N. C., Watts, G. F., and Eckel, R. H. (2019). Statin Toxicity. *Circ. Res.* 124 (2), 328–350. doi:10.1161/CIRCRESAHA.118.312782

Wasserstein, R. L., and Lazar, N. A. (2016). The ASA Statement on P-Values: Context, Process, and Purpose. *American Statistician* 70 (2), 129–133. doi:10.1080/00031305.2016.1154108

WHO Collaboating Centre for Drug Statistics Methodology (2021). Structure and Principles. Available from: https://www.whocc.no/atc/structure_and_principles/.

Wickham, H. (2016). ggplot2: Elegant Graphics Data Anal. *Springer-Verlag N Y*.

Wood, SN (2017). *Generalized Additive Models: An Introduction with R*. 2 ed. Chapman and Hall/CRC.

World Health Organization (2015). *WHO Global Strategy on People-Centred and Integrated Health Services: Interim Report*. World Health Organization. https://apps.who.int/iris/handle/10665/155002.

Yusuf, S, Yusuf, S, Sleight, P, Pogue, J, Bosch, J, Davies, R., et al. (2000). Effects of an Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. *N. Engl. J. Med.* 342 (3), 145–153. doi:10.1056/NEJM200001203420301

Zullig, L. L., Jazowski, S. A., Wang, T. Y., Hellkamp, A., Wojdyla, D., Thomas, L., et al. (2019). Novel Application of Approaches to Predicting Medication Adherence Using Medical Claims Data. *Health Serv. Res.* 54 (6), 1255–1262. doi:10.1111/1475-6773.13200

Conflict of Interest: MJu has received unrestricted grant support from VentureWise (a wholly own commercial subsidiary of NPS MedicineWise) to conduct a commissioned project funded by AstraZeneca. CP is the current Chair of: Kidney Health Australia, NSW Bureau Health Information and the NSW Cardiovascular Research Network, Clinical Trial Steering Committee for CHINA (Baxter); is a Principal International Investigator for the DELIGHT Study, funded by AstraZeneca Sweden); is a member of the International Advisory Board for AstraZeneca; is a member of Local Advisory Boards for Vifor, Merck Sharpe andamp; Dohm, Boehringer Ingelheim and Otsuka, serves on the Scientific Advisory Board of Pharmaxis; has received travel and accommodation support from Amgen, AstraZeneca and Roche; and has received speaker support from Amgen, AstraZeneca, Novartis and Vifor MJa is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Gambro, Baxter and CSL; has served on advisory boards sponsored by Akebia, Astra Zeneca, Baxter, Boehringer Ingelheim, MSD and Vifor, has served/serves on Steering Committees for trials sponsored by Chinook, CSL and Janssen and CSL; leads an investigator-initiated trial with funding support from Dimerix, has spoken at scientific meetings sponsored by Amgen, Janssen, Roche and Vifor; with any consultancy, honoraria or travel support paid to her institution.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 24 March 2022
doi: 10.3389/fphar.2022.836864

Opioid Use at End-Of-Life Among Nova Scotia Patients With Cancer

*Laura V. Minard[1], Judith Fisher[2], Larry Broadfield[3†], Gordon Walsh[3] and Ingrid Sketris[1]**

[1]College of Pharmacy, Dalhousie University, Halifax, NS, Canada, [2]Nova Scotia Department of Health and Wellness, Halifax, NS, Canada, [3]Nova Scotia Health Cancer Care Program, Halifax, NS, Canada

Purpose: To determine the factors associated with opioid analgesic prescriptions as measured by community pharmacy dispensations to all Nova Scotia (NS) patients with cancer at end-of-life from 2005 to 2009.

Methods: The NS Cancer Registry and the NS Prescription Monitoring Program (NSPMP) were used to link Nova Scotians who had a cancer diagnosis and received a prescription for opioids in their last year of life (n = 6,186) from 2005 to 2009. The association of factors with opioid dispensations at end-of-life were determined (e.g., patient demographics, type of prescriber, type of cancer, and opioid type, formulation, and dose).

Results: Almost 54% (n = 6,186) of the end-of-life study population with cancer (n = 11,498) was linked to the NSPMP and therefore dispensed opioids. Most prescriptions were written by general practitioners (89%) and were for strong opioids (81%). Immediate-release formulations were more common than modified-release formulations. Although the annual average parenteral morphine equivalents (MEQ) did not change during the study period, the number of opioid prescriptions per patient per year increased from 5.9 in 2006 to 7.0 in 2009 ($p < 0.0001$). Patients age 80 and over received the fewest prescriptions (mean 3.9/year) and the lowest opioid doses (17.0 MEQ) while patients aged 40–49 received the most prescriptions (mean 14.5/year) and the highest doses of opioid (80.2 MEQ).

Conclusion: Our study examined opioid analgesic use at end-of-life in patients with cancer for a large real-world population and determined factors, trends and patterns associated with type and dose of opioid dispensed. We provide information regarding how general practitioners prescribe opioid therapy to patients at end-of-life. Our data suggest that at the time of this study, there may have been under-prescribing of opioids to patients with cancer at end-of-life. This information can be used to increase awareness among general practitioners, and to inform recommendations from professional regulatory bodies, to aid in managing pain for cancer patients at end-of-life. Future work could address how opioid prescribing has changed over time, and whether efforts to reduce opioid prescribing in response to the opioid crisis have affected patients with cancer at end-of-life in Nova Scotia.

Keywords: palliative, pain control, pharmacy, opioids, cancer, end-of-life (EOL), linked data (data linkage), oncology

OPEN ACCESS

Edited by:
Andrea Burden,
ETH Zürich, Switzerland

Reviewed by:
Andrew Lofts Gray,
University of KwaZulu-Natal, South Africa
Julia Spoendlin,
University of Basel, Switzerland
Kaleen N. Hayes,
Brown University, United States

****Correspondence:***
Ingrid Sketris
mailto:ingrid.sketris@dal.ca

†Deceased

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: *16 December 2021*
Accepted: *07 February 2022*
Published: *24 March 2022*

Citation:
Minard LV, Fisher J, Broadfield L, Walsh G and Sketris I (2022) Opioid Use at End-Of-Life Among Nova Scotia Patients With Cancer. Front. Pharmacol. 13:836864. doi: 10.3389/fphar.2022.836864

INTRODUCTION

Pain is common among persons with cancer. A meta-analysis of 52 studies found that 64% of patients with metastatic or advanced cancer, and 59% of patients in active cancer treatment experienced pain, and more than one-third of patients with pain characterized their pain as moderate or severe (van den Beuken-van Everdingen et al., 2007). Other literature reports that 80–90% of patients with metastatic cancer experience pain, primarily due to tumour infiltration (Christo and Mazloomdoost, 2008; Jost et al., 2010). Cancer survivors may also experience chronic pain that is related to their treatment, such as surgery, chemotherapy or radiation, tissue damage from the malignancy and/or cancer-related conditions (Levy et al., 2008). For example, the incidence of post-surgical chronic pain among breast cancer survivors is estimated to be as high as 50% (Burton et al., 2007).

Strategies exist that can effectively manage cancer-related pain. The World Health Organization (WHO) guidelines for cancer pain management, the "3-step analgesic ladder," position opioids at the second and third steps of the ladder (World Health Organization, 1996). Step 2, for moderate pain, includes weak, immediate-release opioids such as codeine or tramadol, possibly in combination with the non-opioid analgesic, acetaminophen, or a non-steroidal anti-inflammatory drug (Hanks et al., 2001; Krakowski et al., 2003). Strong opioids are recommended for moderate to severe pain (step 3) (World Health Organization, 1996). More recently, many guideline groups have proposed alterations to the WHO analgesic ladder, including deleting the second step, and recommending early use of low dose morphine (Ripamonti et al., 2011; Bandieri et al., 2016; Fallon, 2017; Pain and symptom management, 2017). In addition, there are concerns about using tramadol given its dual mechanism of action, unpredictable metabolism, potential for withdrawal, and toxicities (Young and Juurlink, 2013; Nelson and Juurlink, 2015; Morrow et al., 2019).

Opioid analgesics offer an overall favorable risk to benefit profile (Christo and Mazloomdoost, 2008) and are the mainstay of the pharmacological management of moderate to severe cancer-related pain (Hanks et al., 2001; Krakowski et al., 2003; Henderson, 2017; Pain and symptom management, 2017; Wiffen et al., 2017). A 2017 Cochrane review concluded that with opioid use, approximately 95% of patients with cancer could have their pain reduced from moderate or severe to mild or no pain within 14 days (Wiffen et al., 2017).

Morphine is a strong (step 3) opioid of first choice and the standard against which other opioid analgesics are measured (Hanks et al., 2001). However, patients vary in their response to opioids and some patients may benefit from the use of alternative strong opioids including hydromorphone, oxycodone, fentanyl, and methadone (Breivik, 2001; Hanks et al., 2001). For the majority of patients, the preferred route of administration is oral (Krakowski et al., 2003); however, transdermal, subcutaneous, intramuscular or intravenous routes (occasionally) may be necessary for patients who are unable to take oral medications.

Expert opinion estimates that adequate pain control is possible for 90% of patients with cancer (Cleary, 2007; Deandrea et al., 2008). However, the undertreatment of cancer-related pain is common and a substantial percentage of patients with cancer experience inadequate pain control (Cleary, 2007; Christo and Mazloomdoost, 2008; Deandrea et al., 2008). Barriers to adequate pain management among cancer patients can arise from patient, prescriber, and system level factors (Christo and Mazloomdoost, 2008; Deandrea et al., 2008). The purpose of this study was to 1) determine the use of opioids in Nova Scotia patients with cancer at end-of-life, 2) assess the factors, trends and patterns associated with opioid analgesic prescriptions, and 3) measure opioid dispensing over time from 2005 to 2009.

MATERIALS AND METHODS

This study was approved by the Capital District Health Authority Research Ethics Board, the Nova Scotia Department of Health and Wellness, the Nova Scotia Prescription Monitoring Program Board, and the Cancer Care Nova Scotia Research Committee. Data were de-identified and analyzed after the patient population was deceased; therefore, informed consent was not obtained.

Data Sources

Two data sources used were the Nova Scotia Prescription Monitoring Program database (Nova Scotia Prescription Monitoring Program, 2017) and the Nova Scotia Cancer Registry database (International Association of Cancer Registries, 2018).

The Nova Scotia Prescription Monitoring Program

The Nova Scotia Prescription Monitoring Program (NSPMP) database is an electronic database maintained by Medavie Blue Cross, the organization that administers the province's health insurance program on behalf of the NS government (Nova Scotia Prescription Monitoring Program, 2017). With few exceptions (e.g., products containing tramadol), opioid prescriptions are required by provincial legislation to be reported to the NSPMP. Therefore, the electronic database contains data on most prescription opioid analgesics dispensed by community pharmacies in NS since 1 July 2005. The NSPMP includes comprehensive drug, patient and prescriber related data such as drug name, type, dosage form, quantity dispensed, days supply, patient sex, patient birthdate, and prescriber type (Fisher et al., 2012; Furlan et al., 2014; Nova Scotia Prescription Monitoring Program, 2017). Reporting is completed by the community pharmacy at the time that the prescription is received. Opioid prescriptions for patients residing in long-term care are supplied by community pharmacies and included in the NSPMP while prescriptions for patients admitted to hospital and the limited number of patients who reside in long-term care within the hospital system are supplied by the hospital pharmacy and are not reported to the NSPMP.

The Nova Scotia Cancer Registry

Cancer is a reportable disease in NS. The Nova Scotia Cancer Registry (NSCR) has been collecting data on cancers diagnosed in the province since 1964 (International Association of Cancer

Registries, 2018). The registry excludes non-melanoma skin cancers. The registry contains patient demographics as well as cancer characteristics, such as prognostic information. The International Classification of Diseases for Oncology is used as the standard classification system to define and categorize each new case within the NSCR. Additional reporting guidelines are set out by the Canadian Cancer Registry at Statistics Canada. Each cancer is counted only once, at the time it is diagnosed. This means that if a patient's cancer goes into remission or if the cancer is considered to be under control, but symptoms reappear at a later date it is not counted again. The cause of death is obtained from the death certificate that is provided to the NSCR from the Vital Statistics Unit of Service Nova Scotia, Government of Nova Scotia.

Data Linkage

Processes and procedures to preserve the privacy and confidentiality for the sensitive data present in both data sets were established (**Supplementary Figure S1**). A multi-phased approach was utilized whereby the identification of cases to define the study population was separated from the subsequent construction of the analytic data file. The initial data linkage was undertaken using only identifiers necessary for probabilistic record linkage. No data elements such as prescription data or cancer treatment information were included at the data linkage stage. Furthermore, the analysts involved in the record linkage process were not involved in the data analysis. Conversely, the analysts who conducted the data analysis were not involved in the linkage process and had no access to personal identifiers (Fisher et al., 2011; Broadfield et al., 2018a; Broadfield et al., 2018b; Fisher et al., 2018).

Study Population

The analytical data file included all NS residents diagnosed with cancer from 1991 onward and living in NS during the period 2005–2009. Opioid prescriptions included were those dispensed between 1 July 2005 and 31 December 2009.

Some persons had two or more cancer diagnoses (i.e., two or more cases for one person). In total, there were 53,618 individual persons who had 62,329 tumours (or cases) in the NSCR. The overall linked population consisted of 26,439 cancer cases, representing 25,360 people. For individuals with more than one cancer diagnosis, opioid usage data was assigned only to the most recent case, so 8,711 cases were not assigned any opioid usage by analysis design. Of note, 30,121 cases (or 48% of the total cases) were not linked between the two databases, which indicates that there was no opioid therapy dispensed in community pharmacies for these persons.

The end-of-life study population included those cancer cases that were deceased between 1 July 2006 and 31 December 2009. End-of-life was defined as the last 12 months of life (Victoria State Government and Health and Human Services, 2016). Although we recognize that end-of-life may be shorter or longer than 12 months for the individual patient, we used 12 months to capture a broad range of cancer diagnoses and patients. Opioid prescriptions were restricted to include those dispensed within the 12-month period preceding death. Based on these definitions, 11,498 persons were defined as end-of-life, of which 6,186 (54%) were found in the NSPMP database.

Calculation of Morphine Equivalent Daily Dose

For each cancer case at end-of-life, prescribed daily doses were calculated (University of Manitoba, 2005). The sum of all opioid prescriptions filled in community pharmacies within the 12 months preceding death was determined. Morphine equivalents per day (MEQ) were calculated because different opioids have different potencies. The MEQ is a calculation used to normalize different opioids to a single standard. The MEQ is expressed in milligrams and reported as parenteral morphine equivalents. The morphine equivalents used for morphine, hydromorphone, codeine, and oxycodone were 1, 5 (Alberta Cancer Board, 2001), 0.05 and 0.334, respectively. For fentanyl, 1 mg of drug was considered equivalent to 300 mg of morphine based on a 3-days supply. For each opioid prescription dispensed, the MEQ were calculated by dividing the dispensed quantity by the days' supply and multiplying the quotient by the morphine equivalent associated with the opioid in question. For oral solutions, it was assumed that each dosage was 5 ml, and the dispensed quantity was divided by 5 to make them equivalent with tablet/capsule units. Parenteral dosages were inadvertently divided by 5 due to an error in data analysis. These values were summed for the 12 months preceding death and then divided by the total number of days to derive a daily average. The total number of days was estimated based on the presumed duration of the prescription, which was assumed from the dose and quantity prescribed.

Methadone, dextropropoxyphene, meperidine and pentazocine prescriptions were excluded from these calculations; these agents do not have reliable equianalgesic conversion values, so MEQs cannot be calculated.

Method of Estimation of Chronic Opioid Use

Chronic pain was estimated using duration and amount of opioids. For tablets and oral solutions, chronic use was defined as use of 360 or more tablets/oral agents in a 90-day period. Use of modified-release agents automatically qualified as chronic use.

Data Analysis

The frequency and proportion of persons with cancer at end-of-life dispensed opioid analgesics and their type, quantity, daily dosage, and route of administration were determined. The drugs studied were: morphine (ATC: N02AA01); oxycodone (ATC: N02AA05); fentanyl (ATC: N02AB03); codeine (ATC: R05DA04); hydromorphone (ATC: N02AA03); acetylsalicylic acid/opioid combinations (ATC: N02BA51); acetaminophen/opioid combinations (ATC: N02BE51, N02AA59); methadone (ATC: N07BC02); buprenorphine (ATC: N02AE01) (excludes buprenorphine combination with naloxone (Suboxone) oral tablets (ATC: N07BC51) which are prescribed for opioid dependency); dextropropoxyphene (ATC: N02AC04); meperidine (ATC: N02AB02); and pentazocine (ATC:

N02AD01) (WHO Collaborating Centre for Drug Statistics Methodology, 2009).

The association of the following factors with opioid dispensations at end-of-life was determined:

1) Patient sex,
2) Patient age group at diagnosis by decade (0–29, 30–39,40–49, 50–59, 60–69, 70–79 or 80+). Children and young adults were combined due to the relatively low prevalence of cancers in this group,
3) Patient place of residence by rural/urban designation,
4) Prescriber type: general practitioner or specialist,
5) Cancer site/type was based on the Canadian Cancer Statistics framework (Canadian Cancer Society's Steering Committee, 2010) and classified as follows: oral, esophagus, stomach, colorectal, pancreas, larynx, lung, skin, breast, cervix, body of uterus, ovary, prostate, testis, bladder, kidney, brain, thyroid, non-Hodgkin's lymphoma, Hodgkin's lymphoma, leukemia, liver, multiple myeloma, and other cancers (small bowel, peritoneum and gastrointestinal unspecified, paranasal sinuses, mediastinum, other female genital, penis and male genital unspecified, eye and lacrimal gland, endocrine and other, bone and connective tissue, miscellaneous proliferative disease, other ill defined, unknown primary, and non-melanoma),
6) Prognostic tier was the probability of 5-year survival for each site (Ellison and Wilkins, 2010), with compilation of each site into one of the three groups: high probability of 5-year survival (>80%; tier 1), intermediate probability of 5-year survival (50–80%; tier 2), or low probability of 5-year survival (<50%; tier 3),
7) Opioid formulation: immediate-release (tablets and capsules, powders, suppositories, or oral solutions), modified-release (tablets and capsules, transdermal patches or discs) or miscellaneous, and
8) Type of opioid: strong, weak, or other.

Univariate and multivariate analyses were used to describe opioid use patterns at end-of-life, including the average number of prescriptions and the average MEQ dispensed in the year prior to death. The univariate analysis to estimate the number of opioid prescriptions dispensed within each study period used a person-days at risk method for each of the study covariates including sex, age group at diagnosis, cancer type, prognostic tier and urban or rural residence. Person-days at risk takes exposure time into account. Each person's actual time at-risk is useful for follow-up studies such as ours because exposure time (prognosis) varies by cancer type and other co-variates such as age.

The multivariate analyses were controlled for sex, age group at diagnosis, prognostic tier and urban or rural residence. Cancer type was excluded from the multivariate model because it is highly correlated with prognostic tier.

Univariate regression analyses were used to estimate MEQ consumption for each of the study covariates. Poisson regression analysis was used to model the average number of prescriptions per person per day data, whereas regression analysis was used to model average morphine equivalents per day dispensed per person. Both regression techniques controlled for sex, age group at diagnosis, prognostic tier and urban or rural residence. All univariate and multivariate analyses were conducted using SAS 9.2 (SAS Institute).

RESULTS

Demographics and Clinical Characteristics of Study Population

The demographic and clinical characteristics of the end-of-life study population (n = 11,498) and the end-of-life study population that was linked to the NSPMP (n = 6,186) are shown in **Table 1**. Since the end-of-life study period included deaths occurring between 1 July 2006 and 31 December 2009, there were only half as many deaths in 2006 compared to the other years under investigation. Males were slightly overrepresented (54%) compared to females (46%). Approximately 80% of the end-of-life study population that was linked to the NSPMP were aged 60 and older at the time of their death. The most commonly occurring cancers accounted for the following percentages of all deaths: lung (24%), colorectal (12%), breast (6%), pancreas (5%) and prostate (4%). Patients most commonly had a low probability of 5-year survival (46%; prognostic tier 3). Nearly two-thirds (64%) resided in urban areas at the time of diagnosis.

The year of diagnosis and time between diagnosis and death are shown in **Supplementary Table S1**. Eighty percent of the total end-of-life study population and 85% of the end-of-life study population that was linked to the NSPMP died within 5 years of diagnosis (**Supplementary Table S1**). For both study populations, the average time between diagnosis and death was 2.7 years with a standard deviation of 4.1 years.

Type and Characteristics of Opioid Prescriptions

Prescriber Type

Eighty-nine percent of prescriptions at end-of-life were written by general practitioners while the remaining 11% were written by specialists (**Table 2**).

Drug Type and Formulation

The formulations and types of opioids in the NSPMP that were linked to the end-of-life study population are found in **Table 2**. Approximately 81% of all dispensed opioids were strong opioids and 17% were weak opioids (almost all acetaminophen-opioid combinations). Hydromorphone was the most commonly dispensed opioid (51% of all prescriptions) while morphine was the second most commonly dispensed opioid (19% of all prescriptions). Six percent of all prescriptions were for fentanyl while 4% were for oxycodone and 2% were for codeine. Less than 1% of prescriptions were for opioids that are not recommended for cancer pain (i.e., meperidine, pentazocine and dextropropoxyphene). While 2% of prescriptions were for methadone, it is not known if these were for cancer-related

TABLE 1 | Demographic and clinical characteristics of the end-of-life cancer study populations in Nova Scotia from 2005–2009.

Characteristic	Total end-of life study population n (%)[b]	End-of-life study population linked to NSPMP[a] *n* (%)[c]
Study population	11,498 (100)	6,186 (100)
Year of death		
2006	1,669 (15)	856 (14)
2007	3,331 (29)	1740 (28)
2008	3,307 (29)	1826 (30)
2009	3,191 (28)	1,764 (29)
Sex		
Male	6,222 (54)	3,332 (54)
Female	5,276 (46)	2,854 (46)
Age group at death (years)[d]		
<30	48 (<1)	37 (<1)
30–39	63 (1)	51 (<1)
40–49	351 (3)	279 (5)
50–59	1,043 (9)	803 (13)
60–69	2,132 (19)	1,449 (23)
70–79	3,143 (27)	1742 (28)
80+	4,716 (41)	1824 (29)
Cause of death by cancer site/type		
Oral	112 (1)	87 (1)
Esophagus	210 (2)	142 (2)
Stomach	195 (2)	116 (2)
Colorectal	1,143 (10)	743 (12)
Pancreas	441 (4)	282 (5)
Larynx	51 (<1)	28 (<1)
Lung	2,280 (20)	1,507 (24)
Skin	111 (1)	86 (1)
Breast	506 (4)	363 (6)
Cervix	44 (<1)	33 (<1)
Body of Uterus	100 (1)	53 (<1)
Ovary	176 (2)	104 (2)
Prostate	409 (4)	274 (4)
Bladder	193 (2)	105 (2)
Kidney	204 (2)	136 (2)
Brain	215 (2)	108 (2)
Thyroid	16 (<1)	10 (<1)
Non-Hodgkin's Lymphoma	313 (3)	171 (3)
Hodgkin's Lymphoma	14 (<1)	6 (<1)
Leukemia	277 (2)	115 (2)
Liver	65 (1)	40 (<1)
Multiple Myeloma	124 (1)	89 (1)
Other Cancers	1,140 (10)	618 (10)
Non-Cancer Death	3,159 (27)	970 (16)
Prognostic tier (5-year survival percentage)[e]		
Tier 1 (>80%)	1,285 (11)	848 (14)
Tier 2 (50–80%)	2,510 (22)	1,539 (25)
Tier 3 (<50%)	4,544 (40)	2,829 (46)
Other	3,159 (27)	970 (16)
Region at diagnosis[d]		
Urban	7,291 (63)	3,968 (64)
Rural	4,069 (35)	2,167 (35)

[a]*NSPMP, Nova Scotia Prescription Monitoring Program.*
[b]*Percentage of total end-of-life study population with each characteristic.*
[c]*Percentage of end-of-life study population linked to the NSPMP, with each characteristic.*
[d]*Missing values; numbers may not add up to total study population.*
[e]*Ellison L and Wilkins K. An update on cancer survival. 2010 [cited 11 November 2018]. Statistics Canada, Catalogue no. 82–003-XPE. Health Reports: 21 (3). Available from: https://www150.statcan.gc.ca/n1/en/pub/82-003-x/2010003/article/11334-eng.pdf?st=X1Jalqn3.*

pain or other use (e.g., daily prescriptions for opioid maintenance therapy for dependence). Sixty-six percent of all opioid prescriptions were for immediate-release formulations and 33% were for modified-release products.

Annual Rate of Prescriptions

There was an increasing trend from 2006 to 2009 related to the number of prescriptions received per patient per year in the total end-of-life study population (**Table 3**). In 2006, the adjusted mean number of prescriptions per person per year was 5.9 while in 2009 it was 7.0 ($p < 0.0001$). The mean annual rate of prescriptions did not differ by sex. Older patients (age 80 and over) received the fewest prescriptions (mean 3.9/year) while those age 40–49 received the most (mean 14.5/year). Cancer type had an effect on the number of prescriptions dispensed per year: patients with pancreatic (mean 9.7/year), lung (mean 7.7/year), prostate (mean 7.1/year) or oral (mean 7.0/year) cancer received the greatest mean number of prescriptions per year ($p<0.0001$). Patients in prognostic tier 1 had fewer prescriptions (mean 5.7/year) than those in prognostic tier 2 (mean 6.0/year) or prognostic tier 3 (mean 7.2/year) ($p < 0.0001$). Urban patients received a greater mean number of prescriptions per year (mean 6.3/year) than rural patients (mean 6.2/year) ($p < 0.05$).

Average Morphine Equivalents per Day

The average MEQ for the end-of-life population that was linked to the NSPMP are noted in **Table 4**. There was no difference in adjusted average MEQ from 2006–2009. Males received a higher mean daily dose (27.3 MEQ) compared to females (24.9 MEQ) ($p < 0.01$). Patients aged 80 years and older received lower doses than all other age groups (17.0 MEQ), with the largest dose received by patients aged 40–49 (80.2 MEQ) ($p < 0.0001$). The MEQ varied significantly by cancer type with pancreatic (33.4 MEQ), prostate (33.3 MEQ) and multiple myeloma (31.0 MEQ) receiving the most MEQ ($p < 0.0001$). Patients in prognostic tier 1 received more MEQ (27.1) than those in prognostic tier 2 (26.0) or prognostic tier 3 (26.2). There was no dosage difference in urban versus rural residence at diagnosis.

DISCUSSION

Our study examined opioid analgesic use at end-of-life in patients with cancer for a large real-world population in Nova Scotia and determined factors, trends and patterns associated with type and

TABLE 2 | Profile of opioid dispensations dispensed to the end-of-life cancer study population that was linked to the Nova Scotia Prescription Monitoring Program from 2005–2009.

	n (%)
Total opioid prescriptions	41,222 (100)
Prescriber Type	
General Practitioner	36,542 (89)
Specialist	4,680 (11)
Opioid Formulation	
Immediate-release	27,316 (66)
Tablets or Capsules	22,101 (54)
Parenteral formulations	3,650 (9)
Oral Solutions	1,474 (4)
Syrups	1,456 (4)
Elixirs	18 (<1)
Powders	86 (<1)
Suppositories	5 (<1)
Modified-release	13,747 (33)
Tablets or Capsules	11,088 (27)
Patches	2,516 (6)
Discs	143 (<1)
Miscellaneous[a]	159 (<1)
Type of Opioid	
Strong Opioids	33,193 (81)
Hydromorphone	20,927 (51)
Morphine	7,956 (19)
Fentanyl	2,659 (6)
Oxycodone	1,651 (4)
Weak Opioids	6,855 (17)
Acetaminophen/Opioid Combination	5,953 (14)
Acetylsalicylic Acid/Opioid Combination	9 (<1)
Codeine	893 (2)
Other	1,174 (3)
Methadone	823 (2)
Meperidine	241 (1)
Pentazocine	67 (<1)
Dextropropoxyphene	43 (<1)
Buprenorphine	0 (0)

[a]*Compounds.*

dose of opioid prescribed. There is limited randomized controlled evidence to determine opioid management at end-of-life and our study provides information regarding how prescribers provide opioid therapy in the face of uncertain evidence (Kumar, 2011).

Similar to others, our study found fewer prescriptions per year and lower daily MEQ for older patients. In addition, older patients at end-of-life were less likely to be linked to the NSPMP (i.e., less likely to receive opioid prescriptions): only 39% of patients aged 80 years or older were linked to the NSPMP compared with 64% of patients under age 80. We were unable to determine reasons for this. Patients with cognitive impairment may have difficulty in communicating pain (Ripamonti et al., 2011) and physicians may be reluctant to give higher doses of morphine in older individuals with multiple morbidities. Older patients may also be more likely to be admitted to hospital for end-of-life care and receive opioids in that setting. It is also possible that older patients were more likely to have died due to a cause other than cancer, for which they may not have required opioids. For example, in Canada, cancer and heart disease accounted for approximately half of the deaths in people age 65 and over, and heart disease outranked cancer as the cause of death in people age 85 and older in 2012 (Statistics Canada, 2012).

Our study demonstrated that the majority of encrypted patient identifications linked to the NSPMP at end-of-life were prescribed strong opioids. Opioids that were not recommended in guidelines were rarely used. Some jurisdictions report that physicians are reluctant to use strong opioids (Gao et al., 2014). A Danish study reported only 40% of opioids used by patients with cancer were strong opioids in 1994–1998 (Jarlbaek et al., 2005). Between 2005–2012 in the United Kingdom, 48% of patients with cancer were prescribed a strong opioid in the last year of life (Ziegler et al., 2016). More recently, in Australia, initiation of a strong opioid occurred in 55.8% of patients with cancer and 28.2% of those without cancer between 2013 and 2017 (Lalic et al., 2019). In France in 2012–2016, patients with metastatic bone cancer were found to have an increased dose of strong opioids prescribed once their situation was deemed palliative (Tarot et al., 2021). Our study found that most strong opioid prescriptions were for hydromorphone followed by morphine. In a population-based Ontario study of clinical indications for initiation of opioid therapy, hydromorphone was most commonly prescribed among individuals initiating opioids for cancer or palliative care in 2015–2016 (Pasricha et al., 2018).

Fentanyl patches tend to be used in patients with intolerable morphine side effects or lack of ability to use the oral route, but they are more expensive and have exception criteria for reimbursement on the Nova Scotia Formulary. Fentanyl was used in only 6% of patients in our study. This contrasts with a study of patients with cancer in Taiwan where fentanyl was the opioid prescribed most commonly in 2007 (288 defined daily dose for statistical purposes per million inhabitants per day (S-DDD)), followed by morphine (135 S-DDD) and then codeine (37 S-DDD) (Pan et al., 2013). However, hydromorphone and oxycodone are not available in Taiwan (Pan et al., 2013). In Denmark, fentanyl was used in 11% of patients with cancer in 1998 (Jarlbaek et al., 2005).

Oxycodone was used in 4% of patients. Only 2% of patients received codeine, which is metabolized to morphine in the liver. Codeine may have adverse effects in patients with the CYP2D6 ultrarapid metabolizer phenotype, may be ineffective in poor CYP2D6 metabolizers, and is subject to many drug interactions (Leppert, 2011; Fallon et al., 2018). There was also less than 1% use of meperidine, pentazocine, or dextropropoxyphene which are not recommended as first line drugs.

Our study found that immediate-release formulations of opioids, which are often used for breakthrough pain, were commonly prescribed. Use of immediate-release formulations of opioids is supported by several different recommendations (Global Year against cancer pain 2008-2009, 2015; Potter, 2006).

The average number of opioid prescriptions dispensed to the total end-of-life study population (n = 11,498) increased over the study period from 5.9 to 7.0 ($p < 0.0001$). However, since only 53.8% of the total end-of-life population was linked to the NSPMP (and therefore dispensed opioids), we would expect

TABLE 3 | Adjusted average rate of opioid prescriptions[a] dispensed among the Nova Scotia end-of-life cancer study population from 2005–2009 by selected demographic and clinical characteristics (n = 11,498).

Characteristic	*n*	Adjusted average number of prescriptions per person per year	95% CI	Multivariate Poisson regression results (p-value)
Study population	11,498	—		
Year of death				$p < 0.0001$
2006	1,669	5.9	(5.7–6.2)	
2007	3,331	6.3	(6.1–6.5)	
2008	3,307	6.7	(6.4–6.9)	
2009	3,191	7.0	(6.8–7.3)	
Sex				$p = 0.617$
Male	6,222	6.3	(6.1–6.5)	
Female	5,276	6.3	(6.1–6.5)	
Age group at death (years)[b]				$p < 0.0001$
<30	48	11.4	(10.1–12.8)	
30–39	63	10.3	(9.3–11.3)	
40–49	351	14.5	(13.8–15.1)	
50–59	1,043	11.7	(11.3–12.1)	
60–69	2,132	9.0	(8.7–9.3)	
70–79	3,143	6.3	(6.1–6.5)	
80+	4,716	3.9	(3.7–4.0)	
Cause of death by cancer site/type				$p < 0.0001$
Oral	112	7.0	(6.5–7.5)	
Esophagus	210	6.0	(5.6–6.4)	
Stomach	195	6.7	(6.2–7.2)	
Colorectal	1,143	6.3	(6.1–6.5)	
Pancreas	441	9.7	(9.2–10.2)	
Larynx	51	4.7	(4.1–5.4)	
Lung	2,280	7.7	(7.5–7.9)	
Skin	111	4.2	(3.8–4.6)	
Breast	506	4.9	(4.7–5.2)	
Cervix	44	6.2	(5.5–6.9)	
Body of Uterus	100	4.3	(3.9–4.7)	
Ovary	176	3.9	(3.5–4.2)	
Prostate	409	7.1	(6.8–7.4)	
Bladder	193	5.7	(5.3–6.2)	
Kidney	204	6.3	(5.9–6.7)	
Brain	215	2.5	(2.3–2.8)	
Thyroid	16	6.5	(5.2–8.2)	
Non-Hodgkin's Lymphoma	313	4.0	(3.8–4.3)	
Hodgkin's Lymphoma	14	3.9	(2.8–5.3)	
Leukemia	277	2.2	(2.0–2.4)	
Liver	65	3.9	(3.4–4.5)	
Multiple Myeloma	124	6.1	(5.6–6.6)	
Other Cancers	1,140	6.7	(6.4–6.9)	
Non-Cancer Death	3,159	1.9	(1.8–2.0)	
Prognostic tier (5-year survival percentage)[b]				$p < 0.0001$
Tier 1 (>80%)	1,285	5.7	(5.5–5.8)	
Tier 2 (50–80%)	2,510	6.0	(5.8–6.1)	
Tier 3 (<50%)	4,544	7.2	(7.1–7.4)	
Other	3,159	1.9	(1.9–2.0)	
Region at diagnosisc				$p < 0.05$
Urban	7,291	6.3	(6.1–6.5)	
Rural	4,069	6.2	(5.9–6.4)	

[a]*As estimated from the multivariate model containing all of the above explanatory factors.*

[b]*Ellison L and Wilkins K. An update on cancer survival. 2010 [cited 11 November 2018]. Statistics Canada, Catalogue no. 82–003-XPE. Health Reports:21 (3). Available from: https://www150.statcan.gc.ca/n1/en/pub/82-003-x/2010003/article/11334-eng.pdf?st=X1Jalqn3.*

[c]*Missing values; numbers may not add up to total study population.*

TABLE 4 | Adjusted average morphine equivalents per day (MEQ) dispensed per person among the Nova Scotia end-of-life cancer study population by selected demographic and clinical characteristics from 2005–2009 (n = 6,148).

Characteristic	*n*	Adjusted mean MEQ[a,b,c]	95% CI	Multivariate regression results (*p*-value)
Study population	6,148			
Year of death				$p = 0.12$
2006	847	28.0	(25.0–31.3)	
2007	1,731	27.3	(27.3–30.3)	
2008	1,818	26.7	(24.2–29.6)	
2009	1,752	26.1	(23.5–29.1)	
Sex				$p < 0.01$
Male	3,310	27.3	(24.7–30.3)	
Female	2,838	24.9	(22.4–27.7)	
Age group at death (years)[d]				$p < 0.0001$
<30	37	53.9	(36.5–79.6)	
30–39	51	62.9	(45.1–87.6)	
40–49	278	80.2	(68.2–94.4)	
50–59	801	57.0	(50.6–64.2)	
60–69	1,441	41.8	(37.6–46.4)	
70–79	1730	27.3	(24.7–30.3)	
80+	1809	17.0	(15.2–18.9)	
Cause of death by cancer site/type				$p < 0.0001$
Oral	87	19.4	(15.1–24.9)	
Esophagus	141	21.3	(17.4–25.9)	
Stomach	115	23.0	(18.5–28.6)	
Colorectal	738	27.3	(24.7–30.3)	
Pancreas	282	33.4	(28.8–38.7)	
Larynx	28	24.8	(16.1–38.0)	
Lung	1,502	26.2	(24.1–28.4)	
Skin	86	25.9	(20.1–33.4)	
Breast	361	22.4	(19.4–26.0)	
Cervix	33	24.2	(16.2–36.3)	
Body of Uterus	53	23.8	(17.3–32.8)	
Ovary	104	21.2	(16.7–26.8)	
Prostate	271	33.3	(28.8–38.6)	
Bladder	104	27.2	(21.7–34.1)	
Kidney	134	26.9	(21.9–33.0)	
Brain	107	12.8	(10.2–16.1)	
Thyroid	10	25.7	(12.6–52.4)	
Non-Hodgkin's Lymphoma	170	19.9	(16.6–24.0)	
Hodgkin's Lymphoma	6	16.0	(6.3–40.2)	
Leukemia	114	16.9	(13.5–21.0)	
Liver	40	20.5	(14.3–29.3)	
Multiple Myeloma	89	31.0	(24.2–39.6)	
Other Cancers	614	27.0	(24.2–30.1)	
Non-Cancer Death	959	14.0	(12.7–15.4)	
Prognostic tier (5-year survival percentage)[e]				$p < 0.0001$
Tier 1 (>80%)	843	27.1	(24.4–30.0)	
Tier 2 (50–80%)	1,528	26.0	(23.9–28.3)	
Tier 3 (<50%)	2,818	26.2	(24.4–28.2)	
Other	959	14.2	(12.9–15.7)	
Region at diagnosis				$p = 0.09$
Urban	3,950	27.3	(24.7–30.3)	
Rural	2,147	28.8	(25.9–32.1)	

[a]*MEQ, morphine equivalents per day.*

[b]Parenteral opioids were inadvertently grouped with oral liquids and dosages divided by 5 due to an error in data analysis; however, since parenteral opioids made up 9% of all opioid prescriptions dispensed, we expect this to have minimal effect on the data.
[c]MEQ, used for oxycodone (0.334) and codeine (0.05) were lower than the current standard based on local consideration at the time of the study that these were weaker opioids. These two opioids made up approximately 6% of the total study opioids.
[d]Missing values; numbers may not add up to total study population.
[e]Ellison L and Wilkins K. An update on cancer survival. 2010 [cited 11 Nov 2018]. Statistics Canada, Catalogue no. 82-003-XPE. Health Reports:21(3). Available from: https://www150.statcan.gc.ca/n1/en/pub/82-003-x/2010003/article/11334-eng.pdf?st=X1Jalqn3.

the average number of opioid prescriptions per person per year to be approximately 11–13 for the linked end-of-life population. A study of a health maintenance organization in Israel where patients with cancer receive opioids free of charge noted that these patients received a mean of 5.6 prescriptions per year in 2006 (Shvartzman et al., 2009).

The average MEQ dispensed per patient per year in the end-of-life study population that was linked to the NSPMP ($n = 6,148$) was between 26.1 and 28.0. When these numbers are doubled to calculate oral morphine equivalents, the numbers remain lower than that reported in a study from Israel that found the oral morphine equivalents per day per cancer patient was 113.8 in 2006 (Shvartzman et al., 2009). Similarly, a US study of patients in the 30 days prior to death or hospice enrollment reported higher morphine doses: 85.6 oral morphine milligram equivalents per day in 2007 (Enzinger et al., 2021). However, our results are higher than those found in a Danish study where 10.7 g of oral morphine equivalents per cancer patient per year were used in 1998; this translates to approximately 29.3 MEQ per patient per year (Jarlbaek et al., 2005).

In the wake of the opioid crisis, it is important to reinforce that opioids remain the mainstay of therapy to treat pain in patients with cancer. As health care professional regulatory bodies work to ensure safe opioid prescribing for the broader population (Donroe et al., 2018), physicians may become more reluctant to prescribe opioids and it is possible that there may be unintended consequences of reduced opioid prescribing. This may lead to suboptimal pain management in patients with cancer including those at end-of-life. An Ontario study noted that trends in opioid prescribing may affect patients with or without cancer similarly (Barbera et al., 2018). In spite of the implementation of a provincial symptom screening program with a goal of improving symptom management in patients with cancer, opioid prescription rates did not change in elderly patients with cancer (Barbera et al., 2017). In a younger population, the annual proportion of patients with an opioid prescription decreased from 2004 to 2013 for both cancer and noncancer patients (Barbera et al., 2018). In a US study of Medicare patients with cancer, opioid use in the 30 days prior to death or hospice enrollment declined from 2007 to 2017, while pain-related emergency room visits increased, suggesting that pain control at end-of-life may be worsening in patients with cancer (Enzinger et al., 2021). Similarly, in a US study of patients with solid tumour cancers in the 30 days prior to death, opioid use also declined from 44.7% in 2007–2009 to 26.7% in 2013–2015 (McDermott et al., 2017). One explanation for these findings may be that policies aiming to prevent misuse of opioids have unintentionally led to reduced access to opioids in patients at end-of-life. This may not be limited to patients with cancer. Furuno et al. (2021) found that the frequency of opioid prescribing decreased from 2010 to 2018 in patients being discharged from hospital to hospice care.

A United Kingdom study demonstrated that patients with cancer who receive palliative care were more than twice as likely to receive a strong opioid in the last year of life compared to those who were not provided with palliative care in 2010–2012 (Ziegler et al., 2018). The provision of palliative care in China was also associated with increased prescriptions for strong opioids (Lam et al., 2021). This highlights the role of the palliative care team in ensuring appropriate access to opioids at the end-of-life. However, patients who had not received an opioid prescription were less likely to receive palliative care (Craigs et al., 2018) and in many jurisdictions, access to opioids and palliative care services is limited (Herce et al., 2014; Nambiar et al., 2021; Ngoma et al., 2021).

There may also be evidence of racial inequities in the timing of access to opioids in patients approaching end-of-life (Gurney et al., 2021). In a New Zealand study from 2007 to 2016, 74% of all patients with advanced lung cancer accessed strong opioids within 12 months of diagnosis; however, Maori patients were more likely to first access strong opioids in the 2 weeks prior to death than non-Maori patients (Gurney et al., 2021). These findings highlight that in addition to being cognizant of the special circumstances surrounding opioid prescribing for patients with cancer at end-of-life, prescribers also need to take steps to ensure equitable access to opioids among racialized groups.

Strengths

Our study was a population-based study using a long-established Cancer Registry (active since 1964) linked to the Nova Scotia Prescription Monitoring Program (active since 1992) in which the vast majority of opioids are legislated to be reported. This is the first time these two databases have been linked. We present longitudinal data for both patients with cancer and patients receiving opioids in a province with a longstanding prescription monitoring program. This adds to the evidence related to opioid use by patients with cancer in jurisdictions with a prescription monitoring program (Haffajee et al., 2015; Sproule, 2015; Finley et al., 2017). In addition, we studied an end-of-life cohort. Detailed information on cancer type, prognostic tier and opioid dose, type and route of administration were available. Because we had individual level patient data, we were able to calculate prescribed daily doses (University of Manitoba, 2005) rather than defined daily doses which are a technical unit and reported in some studies when only sales data or pharmacy inventory data are available (Wettermark et al., 2019). We have presented detailed information that can be used for a specific comparison among patients with cancer at end-of-life. In addition, this study provides careful contextual

information for other jurisdictions to do a comparison as it is known that the type of opioid and prescribing rate varies by jurisdiction (Jani et al., 2021). This data may also be useful for palliative care practitioners as they face many challenges, such as an increasing role in managing chronic pain in addition to caring for those with advanced illness, as well as managing and treating addiction (Merlin et al., 2019).

Limitations

The study period was 2005–2009; therefore, opioid prescribing trends may have changed over time. In particular, opioid prescribing may have decreased since this study was conducted as national and regulatory bodies have taken measures to respond to the opioid crisis. For example, a Special Advisory Committee on the Epidemic of Opioid Overdoses was formed in Canada in 2016 in response to the growing opioid crisis (Pan-Canadian Public Health Network, 2021). However, these data can serve as a baseline against which changes in prescribing can be analyzed over time, particularly for patients with cancer in the last year of life.

Opioid use was limited to prescriptions dispensed in community pharmacies within Nova Scotia and did not include any prescriptions dispensed outside the province nor opioids used within hospital settings. Some of the cancer cases that were not linked to the NSPMP may have been in hospital or a palliative care unit which may impact the type and amount of opioid prescribed (Howell et al., 2011).

We were not able to determine whether patients in our study were under-treated with opioids as we did not measure pain control; however, the lower MEQ reported here compared to some other jurisdictions would support this idea. We were unable to determine side effects of the opioids including central nervous system (sedation, confusion, cognitive impairment), gastrointestinal (constipation, nausea, vomiting diarrhea) or other side effects which may have affected the choice of agent (Suh et al., 2004; Wilsey et al., 2010). We were also unable to determine specific physician factors influencing the variation in prescribing including physician characteristics, beliefs and knowledge of pain management for cancer patients at end-of-life (Grant et al., 2009; Mazoyer et al., 2017). We did not study other barriers to opioid prescription such as patient and family attitudes (Jacobsen et al., 2014; Mazoyer et al., 2017; Wright et al., 2019).

We did not look at health service factors changing over time such as the availability of palliative care services or the co-prescription of other treatment modalities such as psychological interventions and physiotherapy. We also did not look at changes in cancer incident rates that may have occurred over the course of this study. The inclusion of non-cancer deaths is a limitation of this study as is the assumption that patients used opioids to treat cancer pain. However, death due to cancer was reported for 84% of patients in this study. Multiple causes of death, and the lack of clinical information to determine whether end-of-life treatment strategies were used, are common limitations that are not specific to studies of patients with cancer (Gershon et al., 2018).

We did not measure concurrent use of multiple opioids, which is sometimes used (e.g., morphine plus hydromorphone) (Lauretti et al., 2003; Gao et al., 2014). We were not able to measure tramadol utilization as tramadol was not included in the NSPMP at the time of this study. Codeine in combination with acetaminophen or acetylsalicylic acid is available without a prescription when the codeine component is 8 mg or less per tablet; therefore, these combination tablets are not monitored under the NSPMP. We did not look at concomitant use of opioids with other adjuvant analgesics (Leppert, 2011). Of note, equianalgesic dose recommendations for the calculation of MEQ have changed over time (Pain and symptom management, 2017; Fallon et al., 2018; Pharmacist's letter, 2012; Government of Canada, 2009).

Future Considerations

Our findings can be used to increase awareness of factors associated with type and dose of opioid prescribed among general practitioners, and to inform opioid standards for professional regulatory bodies to improve pain management in patients with cancer at end-of-life. Future study is needed to assess adherence to standards by general practitioners. Since general practitioners were identified as the primary prescriber of opioids in this population, they should be prioritized for educational programs, audit and feedback, and clinical decision support tools. Our approach can also be used as health systems change their opioid policies and educational interventions. For example, in response to the COVID-19 pandemic, Health Canada issued temporary exemptions under the Controlled Drugs and Substances Act to allow pharmacists to provide continuity of care to vulnerable populations in recognition of the importance of treating chronic pain (Health Canada, 2020). Pharmacist prescribing is one example of an innovative strategy that may be used to improve access to opioids for patients with chronic pain, including those with cancer at end-of-life. Further work is needed to determine the impact of prescribing choices (drug type, route dose, duration, monitoring) on patient pain control and quality of life in patients with cancer at end-of-life. Future study can also address how opioid prescribing has changed over time, and whether efforts to reduce opioid prescribing in response to the opioid crisis have affected patients with cancer at end-of-life in Nova Scotia.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the policies and procedures established by the data steward of the Nova Scotia provincial government, which govern the disclosure of the information in this study, do not allow public sharing of dis-aggregated data. Requests to access the datasets should be directed to Ingrid Sketris, ingrid.sketris@dal.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Capital District Health Authority Research Ethics Board, the Nova Scotia Department of Health and Wellness, the Nova Scotia Prescription Monitoring Program Board, and the Cancer Care Nova Scotia Research Committee. In accordance with the Capital District Health Authority

Research Ethics Board approval, data were de-identified and analyzed after the patient population was deceased; therefore, informed consent was not obtained. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JF, LB and IS contributed to conception and design of the study. GW performed data analysis. All authors contributed to writing the original draft of the manuscript. With the exception of LB (deceased), all authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

The Nova Scotia Cancer Care Program (NSCCP) provided unrestricted funding for the study; although LB and GW work for this funder, the administrators of the NSCCP had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The Drug Evaluation Alliance of Nova Scotia provided salary support to LVM and had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

We acknowledge the Nova Scotia Prescription Monitoring Program for assistance with data analysis. We would like to acknowledge Ron Dewar for assistance with data linkage, Maureen McIntyre for thoughtful comments and Carl Kooker for assistance with literature review. We would like to dedicate this manuscript to LB, deceased October 2016, who always sought to improve the care of patients with cancer.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.836864/full#supplementary-material

REFERENCES

Alberta Cancer Board (2001). *Alberta Hospice Palliative Care Resource Manual*. 2nd ed. [cited 25 Jan 2022]. Available from: http://www.med.uottawa.ca/courses/totalpain/pdf/doc-17.PDF.

Bandieri, E., Romero, M., Ripamonti, C. I., Artioli, F., Sichetti, D., Fanizza, C., et al. (2016). Randomized Trial of Low-Dose Morphine versus Weak Opioids in Moderate Cancer Pain. *J. Clin. Oncol.* 34 (5), 436–442. doi:10.1200/JCO.2015.61.0733

Barbera, L., Sutradhar, R., Chu, A., Seow, H., Howell, D., Earle, C. C., et al. (2018). Comparison of Opioid Prescribing Among Cancer and Noncancer Patients Aged 18-64: Analysis Using Administrative Data. *J. Pain Symptom Manage.* 56 (1), 72–79. doi:10.1016/j.jpainsymman.2018.03.010

Barbera, L., Sutradhar, R., Chu, A., Seow, H., Howell, D., Earle, C. C., et al. (2017). Opioid Prescribing Among Cancer and Non-cancer Patients: Time Trend Analysis in the Elderly Using Administrative Data. *J. Pain Symptom Manage.* 54 (4), 484–e1. doi:10.1016/j.jpainsymman.2017.07.017

Breivik, H. (2001). Opioids in Cancer and Chronic Non-cancer Pain Therapy-Indications and Controversies. *Acta Anaesthesiol Scand.* 45 (9), 1059–1066. doi:10.1034/j.1399-6576.2001.450902.x

Broadfield, L., Fisher, J., Sketris, I., Walsh, G., Dewar, R., MacIntyre, M., et al. (2018). Opioid Analgesic Use Among Nova Scotia (NS) Cancer Patients at the End-Of-Life: Results from a Population-Based Study. Abstract. 2013 [cited 10 Nov 2018]. North American Association of Central Cancer Registries. Available from: https://20tqtx36s1la18rvn82wcmpn-wpengine.netdna-ssl.com/wp-content/uploads/2016/11/2013-Final-Program.pdf.

Broadfield, L., Fisher, J., Sketris, I., and Walsh, G. (2018). Opioid Analgesic Use Among Nova Scotia (NS) Cancer Patients: Results from a Population-Based Observational Study. Abstract. 2012 [cited 10 Nov 2018]. CAPhO. Available from: https://www.capho.org/sites/default/files/nops/NOPS%202012%20Program%20Final_0.pdf.

Burton, A. W., Fanciullo, G. J., Beasley, R. D., and Fisch, M. J. (2007). Chronic Pain in the Cancer Survivor: a New Frontier. *Pain Med.* 8 (2), 189–198. doi:10.1111/j.1526-4637.2006.00220.x

Canadian Cancer Society's Steering Committee (2010). *Canadian Cancer Statistics 2010*. Toronto: Canadian Cancer Society, 105–106. Appendix II: Data Sources and Methods - Table A9.

Christo, P. J., and Mazloomdoost, D. (2008). Cancer Pain and Analgesia. *Ann. N. Y Acad. Sci.* 1138, 278–298. doi:10.1196/annals.1414.033

Cleary, J. F. (2007). The Pharmacologic Management of Cancer Pain. *J. Palliat. Med.* 10 (6), 1369–1394. doi:10.1089/jpm.2007.9842

Craigs, C. L., West, R. M., Hurlow, A., Bennett, M. I., and Ziegler, L. E. (2018). Access to Hospital and Community Palliative Care for Patients with Advanced Cancer: A Longitudinal Population Analysis. *PLoS One* 13 (8), e0200071. doi:10.1371/journal.pone.0200071

Deandrea, S., Montanari, M., Moja, L., and Apolone, G. (2008). Prevalence of Undertreatment in Cancer Pain. A Review of Published Literature. *Ann. Oncol.* 19 (12), 1985–1991. doi:10.1093/annonc/mdn419

Donroe, J. H., Socias, M. E., and Marshall, B. D. L. (2018). The Deepening Opioid Crisis in North America: Historical Context and Current Solutions. *Curr. Addict. Rep.* doi:10.1007/s40429-018-0228-5

Ellison, L., and Wilkins, K. (2010). *An Update on Cancer Survival*. [cited 11 Nov 2018]. Statistics Canada, Catalogue no. 82-003-XPE. Health Reports:21(3). Available from: https://www150.statcan.gc.ca/n1/en/pub/82-003-x/2010003/article/11334-eng.pdf?st=X1Jalqn3.

Enzinger, A. C., Ghosh, K., Keating, N. L., Cutler, D. M., Landrum, M. B., and Wright, A. A. (2021). US Trends in Opioid Access Among Patients with Poor Prognosis Cancer Near the End-Of-Life. *J. Clin. Oncol.* 39 (26), 2948–2958. doi:10.1200/JCO.21.00476

Fallon, M. (2017). Do we Need Step 2 of the WHO Pain Ladder – an EAPC Research Network Study. EAPC abstract book;PS05;36. Madrid: EAPC 2017 [cited 12 Nov 2018]. Available from: http://www.eapc-2017.org/files/EAPC17/dl/EJPC-Abstract-Book-2017.pdf.

Fallon, M., Giusti, R., Aielli, F., Hoskin, P., Rolke, R., Sharma, M., et al. (2018). Management of Cancer Pain in Adult Patients: ESMO Clinical Practice Guidelines. *Ann. Oncol.* 29 (Suppl. l_4), iv166–iv191. doi:10.1093/annonc/mdy152

Finley, E. P., Garcia, A., Rosen, K., McGeary, D., Pugh, M. J., and Potter, J. S. (2017). Evaluating the Impact of Prescription Drug Monitoring Program Implementation: a Scoping Review. *BMC Health Serv. Res.* 17 (1), 420. doi:10.1186/s12913-017-2354-5

Fisher, J., Broadfield, L., MacIntyre, M., Sketris, I. S., Crabtree, K., Dewar, R., et al. (2011). Opioid Use Among Nova Scotia Cancer Patients: Methodology for a Population-Based Observational Study. Poster Session Presented at: the Beatrice Hunter Cancer Research Institute 3rd Annual Cancer Research Conference in Atlantic Canada. Halifax, NS. *November* 7.

Fisher, J., Broadfield, L., Sketris, I., and Walsh, G. (2018). The Impact of Age on the Prevalence and Dose of Opioid Analgesics in Patients with Cancer at End-Of-Life: A Population Based Study. Abstract. 2013 [cited 10 Nov 2018]. Canadian Association of Gerontology. Available from: https://cag.conference-services.net/reports/template/onetextabstract.xml?xsl=template/onetextabstract.xsl&conferenceID=3546&abstractID=753630.

Fisher, J. E., Zhang, Y., Sketris, I., Johnston, G., and Burge, F. (2012). The Effect of an Educational Intervention on Meperidine Use in Nova Scotia, Canada: a Time Series Analysis. *Pharmacoepidemiol. Drug Saf.* 21 (2), 177–183. doi:10.1002/pds.2259

Furlan, A. D., MacDougall, P., Pellerin, D., Shaw, K., Spitzig, D., Wilson, G., et al. (2014). Overview of Four Prescription Monitoring/review Programs in Canada. *Pain Res. Manag.* 19 (2), 102–106. doi:10.1155/2014/634171

Furuno, J. P., Noble, B. N., Fromme, E. K., Hartung, D. M., Tjia, J., Lynn, M., et al. (2021). Decreasing Trends in Opioid Prescribing on Discharge to Hospice Care. *J. Pain Symptom Manage.* 62 (5), 1026–1033. doi:10.1016/j.jpainsymman.2021.03.025

Gao, W., Gulliford, M., Bennett, M. I., Murtagh, F. E., and Higginson, I. J. (2014). Managing Cancer Pain at the End of Life with Multiple strong Opioids: A Population-Based Retrospective Cohort Study in Primary Care. *PLoS One* 9 (1), e79266. doi:10.1371/journal.pone.0079266

Gershon, A. S., Maclagan, L. C., Luo, J., To, T., Kendzerska, T., Stanbrook, M. B., et al. (2018). End-of-life Strategies Among Patients with Advanced Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* 198 (11), 1389–1396. doi:10.1164/rccm.201803-0592OC

Global Year against cancer pain 2008-2009 (2015). International Association for the Study of Pain. Available from: https://www.iasp-pain.org/GlobalYear/CancerPain.

Government of Canada (2009). *Recalls and Safety Alerts. Important Changes to the Dose Conversion Guidelines for Fentanyl Transdermal Systems – for Health Professionals.* [cited 19 Nov 2020]. Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2009/14548a-eng.php.

Grant, M., Elk, R., Ferrell, B., Morrison, R. S., and von Gunten, C. F. (2009). Current Status of Palliative Care-Cclinical Implementation, Education, and Research. *CA Cancer J. Clin.* 59 (5), 327–335. doi:10.3322/caac.20032

Gurney, J. K., Stanley, J., Adler, J., McLeod, H., Atkinson, J., and Sarfati, D. (2021). National Study of Pain Medicine Access Among Māori and Non-māori Patients with Lung Cancer in New Zealand. *JCO Glob. Oncol.* 7, 1276–1285. doi:10.1200/GO.21.00141

Haffajee, R. L., Jena, A. B., and Weiner, S. G. (2015). Mandatory Use of Prescription Drug Monitoring Programs. *JAMA* 313 (9), 891–892. doi:10.1001/jama.2014.18514

Hanks, G. W., Conno, F., Cherny, N., Hanna, M., Kalso, E., McQuay, H. J., et al. (2001). Morphine and Alternative Opioids in Cancer Pain: the EAPC Recommendations. *Br. J. Cancer* 84 (5), 587–593. doi:10.1054/bjoc.2001.1680

Health Canada (2020). *Subsection 56(1) Class Exemption for Patients, Practitioners and Pharmacists Prescribing and Providing Controlled Substance in Canada during the Coronavirus Pandemic*. Mar 19 [cited 15 Dec 2021]. Available from: https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/CDSA_exemption.pdf.

Henderson, D. (2017). *Appeal to Physicians – Opioids Have Their Place: Let's Avoid an Unintended Tragedy!*. CMAJ. 6 Nov 2017 [cited 10 Nov 2018]. Available from: http://www.cmaj.ca/content/appeal-physicians-opioids-have-their-place-lets-avoid-unintended-tragedy.

Herce, M. E., Elmore, S. N., Kalanga, N., Keck, J. W., Wroe, E. B., Phiri, A., et al. (2014). Assessing and Responding to Palliative Care Needs in Rural Sub-saharan Africa: Results from a Model Intervention and Situation Analysis in Malawi. *PLoS One* 9 (10), e110457. doi:10.1371/journal.pone.0110457

Howell, D., Marshall, D., Brazil, K., Taniguchi, A., Howard, M., Foster, G., et al. (2011). A Shared Care Model Pilot for Palliative home Care in a Rural Area: Impact on Symptoms, Distress, and Place of Death. *J. Pain Symptom Manage.* 42 (1), 60–75. doi:10.1016/j.jpainsymman.2010.09.022

International Association of Cancer Registries (2018). Nova Scotia Cancer Registry Profile Page. [cited 10 Nov 2018]. Available from: http://www.iacr.com.fr/index.php?option=com_comprofiler&task=userprofile&user=892&Itemid=498.

Jacobsen, R., Samsanaviciene, J., Liubarskiene, Z., Sjøgren, P., Møldrup, C., Christrup, L., et al. (2014). Barriers to Cancer Pain Management in Danish and Lithuanian Patients Treated in Pain and Palliative Care Units. *Pain Manag. Nurs.* 15 (1), 51–58. doi:10.1016/j.pmn.2012.06.002

Jani, M., Girard, N., Bates, D. W., Buckeridge, D. L., Sheppard, T., Li, J., et al. (2021). Opioid Prescribing Among New Users for Non-cancer Pain in the USA, Canada, UK, and Taiwan: A Population-Based Cohort Study. *Plos Med.* 18 (11), e1003829. doi:10.1371/journal.pmed.1003829

Jarlbaek, L., Andersen, M., Hallas, J., Engholm, G., and Kragstrup, J. (2005). Use of Opioids in a Danish Population-Based Cohort of Cancer Patients. *J. Pain Symptom Manage.* 29 (4), 336–343. doi:10.1016/j.jpainsymman.2004.07.010

Jost, L., Roila, F., and Esmo Guidelines Working Group (2010). Management of Cancer Pain: ESMO Clinical Practice Guidelines. *Ann. Oncol.* 21 (Suppl. 5), v257–60. doi:10.1093/annonc/mdq224

Krakowski, I., Theobald, S., Balp, L., Bonnefoi, M. P., Chvetzoff, G., Collard, O., et al. (2003). Summary Version of the Standards, Options and Recommendations for the Use of Analgesia for the Treatment of Nociceptive Pain in Adults with Cancer (Update 2002). *Br. J. Cancer* 89 (Suppl. 1), S67–S72. doi:10.1038/sj.bjc.6601086

Kumar, S. P. (2011). Reporting Characteristics of Cancer Pain: a Systematic Review and Quantitative Analysis of Research Publications in Palliative Care Journals. *Indian J. Palliat. Care* 17 (1), 57–66. doi:10.4103/0973-1075.78451

Lalic, S., Ilomäki, J., Bell, J. S., Korhonen, M. J., and Gisev, N. (2019). Prevalence and Incidence of Prescription Opioid Analgesic Use in Australia. *Br. J. Clin. Pharmacol.* 85 (1), 202–215. doi:10.1111/bcp.13792

Lam, T. C., Chan, S. K., Choi, C. W., Tsang, K. C., Yuen, K. K., Soong, I., et al. (2021). Integrative Palliative Care Service Model Improved End-Of-Life Care and Overall Survival of Advanced Cancer Patients in Hong Kong: A Review of Ten-Year Territory-wide Cohort. *J. Palliat. Med.* 24 (9), 1314–1320. doi:10.1089/jpm.2020.0640

Lauretti, G. R., Oliveira, G. M., and Pereira, N. L. (2003). Comparison of Sustained-Release Morphine with Sustained-Release Oxycodone in Advanced Cancer Patients. *Br. J. Cancer* 89 (11), 2027–2030. doi:10.1038/sj.bjc.6601365

Leppert, W. (2011). Pain Management in Patients with Cancer: Focus on Opioid Analgesics. *Curr. Pain Headache Rep.* 15 (4), 271–279. doi:10.1007/s11916-011-0201-7

Levy, M. H., Chwistek, M., and Mehta, R. S. (2008). Management of Chronic Pain in Cancer Survivors. *Cancer J.* 14 (6), 401–409. doi:10.1097/PPO.0b013e31818f5aa7

Mazoyer, J., Sastre, M. T. M., Sorum, P. C., and Mullet, E. (2017). Mapping French People and Health Professionals' Positions Regarding the Circumstances of Morphine Use to Relieve Cancer Pain. *Support Care Cancer* 25 (9), 2723–2731. doi:10.1007/s00520-017-3682-z

McDermott, C. L., Fedorenko, C., Kreizenbeck, K., Sun, Q., Smith, B., Curtis, J. R., et al. (2017). End-of-life Services Among Patients with Cancer: Evidence from Cancer Registry Records Linked with Commercial Health Insurance Claims. *J. Oncol. Pract.* 13 (11), e889–99. doi:10.1200/JOP.2017.021683

Merlin, J. S., Patel, K., Thompson, N., Kapo, J., Keefe, F., Liebschutz, J., et al. (2019). Managing Chronic Pain in Cancer Survivors Prescribed Long-Term Opioid Therapy: A National Survey of Ambulatory Palliative Care Providers. *J. Pain Symptom Manage.* 57 (1), 20–27. doi:10.1016/j.jpainsymman.2018.10.493

Morrow, R. L., Dormuth, C. R., Paterson, M., Mamdani, M. M., Gomes, T., and Juurlink, D. N. (2019). Tramadol and the Risk of Seizure: Nested Case-Control Study of US Patients with Employer-Sponsored Health Benefits. *BMJ Open* 9 (3), e026705. doi:10.1136/bmjopen-2018-026705

Nambiar, A. R., Rana, S., and Rajagopal, M. R. (2021). Serious Health-Related Suffering and Palliative Care in South Asian Countries. *Curr. Opin. Support. Palliat. Care* 15 (3), 169–173. doi:10.1097/SPC.0000000000000565

Nelson, L. S., and Juurlink, D. N. (2015). Tramadol and Hypoglycemia: One More Thing to Worry about. *JAMA Intern. Med.* 175 (2), 194–195. doi:10.1001/jamainternmed.2014.5260

Ngoma, M., Mushi, B., Morse, R. S., Ngoma, T., Mahuna, H., Lambden, K., et al. (2021). mPalliative Care Link: Examination of a mobile Solution to Palliative Care Coordination Among Tanzanian Patients with Cancer. *JCO Glob. Oncol.* 7, 1306–1315. doi:10.1200/GO.21.00122

Nova Scotia Prescription Monitoring Program (2017). About Us: History. [cited 22 June 2010]. Available from: http://www.nspmp.ca/history.php.

Pain and symptom management (2017). *BC Guidelines [Internet]*. [cited 17 Nov 2020]. British Columbia. Available from: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/palliative2_pain.pdf.

Pan, H. H., Ho, S. T., Lu, C. C., Wang, J. O., Lin, T. C., and Wang, K. Y. (2013). Trends in the Consumption of Opioid Analgesics in Taiwan from 2002 to 2007: a Population-Based Study. *J. Pain Symptom Manage.* 45 (2), 272–278. doi:10.1016/j.jpainsymman.2012.02.014

Pan-Canadian Public Health Network (2021). *Special Advisory Committee on the Epidemic of Opioid Overdoses*. Mar [cited 25 Jan 2022]. Available from: http://www.phn-rsp.ca/sac-opioid-gcs-opioides/index-eng.php.

Pasricha, S. V., Tadrous, M., Khuu, W., Juurlink, D. N., Mamdani, M. M., Paterson, J. M., et al. (2018). Clinical Indications Associated with Opioid Initiation for Pain Management in Ontario, Canada: A Population-Based Cohort Study. *Pain* 159 (8), 1562–1568. doi:10.1097/j.pain.0000000000001242

Pharmacist's letter (2012). *Equianalgesic Dosing of Opioids for Pain Management*. [cited 19 Nov 2020]. Available from: https://www.nhms.org/sites/default/files/Pdfs/Opioid-Comparison-Chart-Prescriber-Letter-2012.pdf.

Potter, M. B. (2006). Opioids for Management of Breakthrough Pain in Cancer Patients. *Am. Fam. Physician* 74 (11), 1855–1857.

Ripamonti, C. I., Bandieri, E., and Roila, F. (2011). Management of Cancer Pain: ESMO Clinical Practice Guidelines. *Ann. Oncol.* 22 Suppl 6 (Suppl. 6), vi69–77. doi:10.1093/annonc/mdr390

Shvartzman, P., Freud, T., Singer, Y., Brill, S., Sherf, M., Battat, E., et al. (2009). Opioid Use in an Israeli Health Maintenance Organization: 2000-2006. *Pain Med.* 10 (4), 702–707. doi:10.1111/j.1526-4637.2009.00621.x

Sproule, B. (2015). *Prescription Monitoring Programs in Canada: Best Practice and Program Review*. Ottawa, ON: Canadian Centre on Substance Abuse. [cited 12 Nov 2018]. Available from: http://www.ccsa.ca/Resource%20Library/CCSA-Prescription-Monitoring-Programs-in-Canada-Report-2015-en.pdf.

Statistics Canada (2012). The 10 Leading Causes of Death. CANSIM (death database) [internet]. Ottawa (ON): Statistics Canada; 2015 Dec 10 [cited 25 Jan 2022]. Available from: https://www150.statcan.gc.ca/n1/pub/82-625-x/2015001/article/14296-eng.htm.

Suh, E. S., Bartlett, G., Inguanti, M., and Folstad, J. (2004). Evaluation of a Pharmacist Pain Management Education Program and Associated Medication Use in a Palliative Care Population. *Am. J. Health Syst. Pharm.* 61 (3), 277–280. doi:10.1093/ajhp/61.3.277

Tarot, A., Delorme, J., Authier, N., and Guastella, V. (2021). Opioid Prescriptions in Bone Metastatic Cancer Patients: A Cross Sectional Nationwide Pharmacoepidemiological Study. *Bull. Cancer* 108 (12), 1120–1125.

University of Manitoba (2005). *Concept Dictionary and Glossary. Term: Prescribed Daily Dose (PDD)*. Nov [cited 25 Jan 2022]. Available from: http://mchp-appserv.cpe.umanitoba.ca/viewDefinition.php?definitionID=103383.

van den Beuken-van Everdingen, M. H., de Rijke, J. M., Kessels, A. G., Schouten, H. C., van Kleef, M., and Patijn, J. (2007). Prevalence of Pain in Patients with Cancer: a Systematic Review of the Past 40 Years. *Ann. Oncol.* 18 (9), 1437–1449. doi:10.1093/annonc/mdm056

Victoria State Government, Health and Human Services (2016). *Victoria's End of Life and Palliative Care Framework*. Jun [cited 25 Jan 2022]. Available from: https://www.health.vic.gov.au/patient-care/victorias-end-of-life-and-palliative-care-framework.

Wettermark, B., Vlahović-Palčevski, V., LeeBergman, D. U., and Bergman, U. (2019). "Studies of Drug Utilization," in *Studies of Drug Utilization" in Pharmacoepidemiology*. Editors B. L. Strom, S. E. Kimmel, and S. Hennessy. Sixth Edition (John Wiley & Sons), 373–410. Chapter 18. doi:10.1002/9781119413431.ch18

Who Collaborating Centre for Drug Statistics Methodology (2009). *Definitions and General Considerations*. [cited 27 Jan 2011]. Available from: http://www.whocc.no/ddd/definition_and_general_considera/.

Wiffen, P. J., Wee, B., Derry, S., Bell, R. F., and Moore, R. A. (2017). Opioids for Cancer Pain - an Overview of Cochrane Reviews. *Cochrane Database Syst. Rev.* 7, CD012592. doi:10.1002/14651858.CD012592.pub2

Wilsey, B. L., Fishman, S. M., Casamalhuapa, C., and Singh, N. (2010). Computerized Progress Notes for Chronic Pain Patients Receiving Opioids; the Prescription Opioid Documentation System (PODS). *Pain Med.* 11 (11), 1707–1717. doi:10.1111/j.1526-4637.2010.00977.x

World Health Organization (1996). *Cancer Pain Relief: With a Guide to Opioid Availability*. 2nd ed. Geneva: World Health Organization.

Wright, E. M., El-Jawahri, A., Temel, J. S., Carr, A., Safren, S. A., Park, E. R., et al. (2019). Patient Patterns and Perspectives on Using Opioid Regimens for Chronic Cancer Pain. *J. Pain Symptom Manage.* 57 (6), 1062–1070. doi:10.1016/j.jpainsymman.2019.02.023

Young, J. W. S., and Juurlink, D. N. (2013). Tramadol. *Cmaj* 185 (8), E352. doi:10.1503/cmaj.121592

Ziegler, L., Mulvey, M., Blenkinsopp, A., Petty, D., and Bennett, M. I. (2016). Opioid Prescribing for Patients with Cancer in the Last Year of Life: A Longitudinal Population Cohort Study. *Pain* 157 (11), 2445–2451. doi:10.1097/j.pain.0000000000000656

Ziegler, L. E., Craigs, C. L., West, R. M., Carder, P., Hurlow, A., Millares-Martin, P., et al. (2018). Is Palliative Care Support Associated with Better Quality End-Of-Life Care Indicators for Patients with Advanced Cancer? A Retrospective Cohort Study. *BMJ Open* 8 (1), e018284. doi:10.1136/bmjopen-2017-018284

Conflict of Interest: IS is a member of the Patented Medicines Prices Review Board. IS holds unrestricted grants from CIHR and the Nova Scotia Department of Health and Wellness.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 25 March 2022
doi: 10.3389/fphar.2022.869162

Integrating Pharmacy and Registry Data Strengthens Clinical Assessments of Patient Adherence

Sarah Serhal[1,2]*, *Carol Armour*[1,3], *Laurent Billot*[4,5], *Ines Krass*[2], *Lynne Emmerton*[6], *Bandana Saini*[1,2], *Sinthia Bosnic-Anticevich*[1,3], *Bonnie Bereznicki*[7], *Luke Bereznicki*[8], *Sana Shan*[4] *and Anna Campain*[4,5]

[1]Woolcock Institute of Medical Research, Sydney, NSW, Australia, [2]School of Pharmacy, The University of Sydney, Sydney, NSW, Australia, [3]Central Sydney Area Health Service, Sydney, NSW, Australia, [4]The George Institute, Newtown, NSW, Australia, [5]Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia, [6]Curtin Medical School, Curtin University, Perth, WA, Australia, [7]Tasmanian School of Medicine, Hobart, TAS, Australia, [8]School of Pharmacy and Pharmacology, University of Tasmania, Hobart, TAS, Australia

Background: Accurate clinical assessment of patient adherence using reliable and valid measures is essential in establishing the presence of adherence issues and support practices for pharmacists.

Objective: This investigation aims to conduct a novel assessment of patient adherence to asthma controller therapy by combining 1) patient-specific dosage data found in pharmacy dispensing data with 2) centrally collected administrative claims records, to determine the added value of using both sources of data.

Methods: A total of 381 clinically uncontrolled asthma patients, from 95 community pharmacies across three Australian States were recruited and provided consent for the retrieval of their claims records and pharmacy dispensing data. Patients were stratified as multiple or single pharmacy users and adherence scores were calculated *via* the proportion of days covered (PDC) method using 1) patient claims records, 2) patient pharmacy dispensing data, and 3) combined claims records and pharmacy dispensing data. Cohort and subgroup adherence estimates were then compared.

Results: Low levels of adherence were evident amongst the cohort irrespective of the data source used. PDC estimates based on claims records alone or combined claims records and pharmacy dispensing data were significantly higher than estimates based on pharmacy dispensing data for the total cohort (56%, 52%, 42% respectively, $p < 0.001$) and more noticeably for multiple pharmacy users (67%, 64%, 35% respectively, $p < 0.001$). PDC estimates based on combined claims records and pharmacy dispensing data were significantly lower than estimates based on claims records alone, indicating that perhaps standard daily dose is not a robust proxy for prescribed dosage to inhaled respiratory devices in adherence approximations. Poorer adherence was found amongst single pharmacy users

OPEN ACCESS

Edited by:
Mina Tadrous,
Women's College Hospital, Canada

Reviewed by:
Mohamed Amin,
AlAlamein International University, Egypt
Long Ming,
Universiti Brunei Darussalam, Brunei

***Correspondence:**
Sarah Serhal
sarah.serhal@sydney.edu.au

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: *03 February 2022*
Accepted: *28 February 2022*
Published: *25 March 2022*

Citation:
Serhal S, Armour C, Billot L, Krass I, Emmerton L, Saini B, Bosnic-Anticevich S, Bereznicki B, Bereznicki L, Shan S and Campain A (2022) Integrating Pharmacy and Registry Data Strengthens Clinical Assessments of Patient Adherence. Front. Pharmacol. 13:869162. doi: 10.3389/fphar.2022.869162

Abbreviations: SES, Absolute standardized effect sizes; ACQ, Asthma control questionnaire; IAQLQ, Impact of asthma on quality-of-life questionnaire; IQR, Interquartile range; PBS, Pharmaceutical Benefits Scheme; PTP-ARC, Pharmacy Trial Program—Asthma and Rhinitis Control; PDC, Proportion of days covered; RCAT, Rhinitis control assessment test; SD, Standard deviation; WRS, Wilcoxon Rank Sum.

than multiple pharmacy users when combined claims records and pharmacy dispensing data (46% compared to 64% respectively, $p < 0.001$) or claims records alone (51% compared to 67% respectively, $p < 0.001$) were compared.

Conclusion: Access to routine collected data increases clinical acuity over patient adherence to asthma controller medications and is a valuable resource for health care professionals. A policy of secure accessibility of such data at the patient-pharmacist or patient-GP interface may allow real-time intervention and assist in decision making across numerous therapeutic areas.

Keywords: asthma, medication adherence, data linkage, pharmacy, primary care, routinely collected data, pharmacy refill data, pharmaceutical benefits scheme

INTRODUCTION

Suboptimal medication adherence is an intractable issue that compromises patient care. Maintaining optimal adherence is a challenge regardless of the medication or the nature of the illness (Eduardo Sabaté, 2003; Elliott et al., 2006; Yeaw et al., 2009). In recent decades, long-term medication adherence for chronic conditions has been estimated to be less than 50% (Eduardo Sabaté, 2003), with predictions of this adherence gap to widen as the global population ages (Elliott et al., 2006). Poor adherence negatively impacts a patient's health, reduces the effectiveness of treatments, and increases financial burden on patients and the health system (Haynes et al., 2008; National Collaborating Centre for Primary, 2009; Golay, 2011; GuildLink, 2021). Thus improving medication adherence is a public health concern and may benefit population health outcomes and health economics (Golay, 2011; Marcum et al., 2017; Torres-Robles et al., 2021).

Increasingly, healthcare is becoming more digitalized and large health databases are being used within pharmacoepidemiologic cohort-based research for measuring population adherence (The Organisation for Economic Co-operation and Development, 2019; The Commonwealth Fund, 2021). Sources of routinely collected medication registry data include prescribing or dispensing data, health insurance data and national health records (Kardas et al., 2020). These registry data contain five elements: 1) the drug name, 2) strength, 3) dose, 4) quantity, and 5) date of dispensing (Schneeweiss and Avorn, 2005). National health records, including routinely collected national pharmacy claims records (henceforth referred to as claims records), are often collected for national administrative purposes and are therefore accurate, unified and complete, but may lack prescribed dosage information. When using claims records, adherence estimates are based on guideline-specified (standard) doses that may not be representative of the patient's prescribed medication regimen.

Within community pharmacy, a unique opportunity exists to detect suboptimal adherence among patients. For example, pharmacist vigilance in monitoring medication usage could prompt pharmacist-led interventions to address patient-specific adherence barriers affecting asthma control (Chan et al., 2013) and/or can enable pharmacists to effectively triage patients to appropriate care by their clinicians. Within community pharmacy, using pharmacy dispensing data to calculate medication possession rates and coverage is clinically convenient and useful (Lehmann et al., 2014). Pharmacy dispensing data are extremely valuable as they include prescribed dosage details for each patient. However, these data report exclusively what was collected at a single pharmacy. Therefore, this measure may underestimate a patient's adherence, particularly if patients visit multiple pharmacies for convenience, or personal, clinical or financial reasons (Sansone and Sansone, 2012). In Australia, it is estimated that approximately one quarter of patients visit multiple pharmacies for their prescription medication needs, increasing to one third for other non-prescription medicines (The Pharmacy Guild of Australia, 2018; Pearson DDL, 2021).

Asthma is an incurable chronic inflammatory condition of the airways. For most patients, consistent use of preventative therapy (controller medicines) is needed to achieve symptomatic control and better health-related quality of life and minimize future exacerbation risk (National Asthma Council Australia, 2019; Global Initiative for Asthma, 2020). Like many chronic diseases, suboptimal levels of adherence amongst adults with asthma is well documented internationally (DiSantostefano et al., 2013; Reddel et al., 2015; Hull et al., 2016; Australian Institute of Health and Welfare, 2018; Cutler et al., 2018; Amin et al., 2020). However, provision of adherence support by pharmacists has been shown to improve therapeutic outcomes (Armour et al., 2007; Chan et al., 2013; Torres-Robles et al., 2021).

Through advances in e-health technology in some countries, claims records are becoming more accessible to healthcare providers *via* patient e-health records, including within community pharmacy. Thus, in the absence of a gold standard for estimating patient adherence and assisted by the knowledge that all asthma controller medicines are recorded through claims records, there is an opportunity to utilize both pharmacy dispensing data and claims records to gain a more complete understanding of a patient's adherence to asthma controller therapy. This will enable pharmacists to efficiently direct adherence-based interventions to those most in need.

Previous studies have attempted to expand this field and ascertain adherence patterns such as the prevalence of primary

non-adherence by linking general practice prescribing and pharmacy dispensing data or pharmaceutical claims records and hospitalization data (Linnet et al., 2012; Tibble et al., 2020). To the best of our knowledge this is the first study to have access to a linked set of pharmacy dispensing data and pharmaceutical claims records for a cohort of patients. Additionally, it is the first time these data sources have been combined to create a novel measure of adherence that can be compared to traditionally used methods. This investigation aimed to conduct a novel assessment of patient adherence to asthma controller therapy by combining 1) patient-specific dosage data found in pharmacy dispensing data with 2) claims records. The overall objective was to determine if the novel measure provided a clearer indication of a patient's medication adherence and to establish a potential framework for the use of routinely collected claims data in practice.

MATERIALS AND METHODS

This study used pharmacy dispensing data and routinely collected national pharmacy claims records relating to participants in the Pharmacy Trial Program–Asthma and Rhinitis Control (PTP-ARC) (Australian Government Department of Health, 2021; Serhal et al., 2021).

A total of 381 patients, from 95 regional, remote, and metropolitan community pharmacies in the Australian states of New South Wales (NSW), Western Australia (WA) and Tasmania were recruited between August 2018 and March 2019 (Australian Government Department of Health, 2021; Serhal et al., 2021). Patients were adults aged 18 years or older with a current diagnosis of asthma. Among other variables, the PTP-ARC measured patients' medication adherence to asthma controller therapy in the 12 months prior to enrolment in the PTP-ARC, whereupon their asthma was assessed as poorly controlled in accordance with the Asthma Control Questionnaire (ACQ score of 1.5 or over) (Juniper et al., 1999; Juniper et al., 2006).

The trial was approved by the Human Research Ethics Committees of The University of Sydney, Curtin University and The University of Tasmania, funded by the Australian Government Department of Health (Australian New Zealand Clinical Trials Registry, 2018) and registered within the Australian New Zealand Clinical Trials Registry (Registration Number ACTRN12618000313235) (Australian Government Department of Health, 2021). All participating patients provided informed consent to participate in the study and for retrieval of their medication collection records.

Data Sources

This study uses two data sources including 1) claims records and 2) pharmacy dispensing data.

(1) Claims records are routinely collected administrative data obtained by the Australian government as part of their subsidization scheme for prescription medicines known as the Pharmaceutical Benefits Scheme (PBS) (Australian Government Department of Health, 2021). Claims records are a national data source and all medication dispensed through the PBS, within an Australian pharmacy, are recorded in a central database upon submission for reimbursement and can be linked to a patient *via* their unique Medicare ID (Australian Government Department of Health, 2021). PBS medicines are subject to a patient co-payment to a threshold amount based on patient concessional status. This dataset includes medicines both below and above this threshold (excluding items dispensed as "private" or those not on the PBS List). Separate consent was requested for collection of patient pharmaceutical claims records. Services Australia (formerly the Department of Human Services) is acknowledged for supplying the PBS information.

(2) Pharmacy dispensing data are records of all medications collected by patients from a particular pharmacy. This data is specific to the pharmacy site in which the medications were collected and are kept locally to form part of a patients records and for legal and reimbursement purposes.

All data collected for the purposes of this investigation were deidentified.

Although these data sources are similar, key differences are present in both coverage (national vs. individual pharmacies) and the presence of prescribed dosage information supplied by the treating clinician. These differences are summarized in **Table 1**.

Calculating Adherence

Adherence scores were calculated for each patient using the proportion of days covered (PDC). This measure refers to the proportion of days that a patient would have access to medicines based on the amount of medication dispensed, and is a measure between 0 and 100% (Raebel et al., 2013; National Center for Chronic Disease Prevention and Health Promotion, 2015; American Pharmacist Association, 2020). A PDC of 80% or higher represented adherence to controller therapy, and lower than 80% as non-adherence to controller therapy (Karve et al., 2009; Raebel et al., 2013).

$$PDC\ (\%) = \left(\frac{Number\ of\ days\ with\ medication\ available}{Number\ of\ days\ in\ the\ period}\right) x\ 100$$

This calculation was performed using 1) claims records, 2) pharmacy dispensing data, and 3) combined claims records and pharmacy dispensing data.

Adherence Calculated *via* Claims Records

A complete 12-month national pharmacy claims history was collected for all consenting patients. Number of days with medication available was based on the date of medication supply and the number of doses supplied. Standard daily dosing was assumed due to data limitations with respect to prescribed dosage. Standard dose is defined as the minimum effective dose for adults required for each formulation/product,

based on recommendations provided by the Australia Medicines Handbook (Australian Medicines Handbook, 2020), Therapeutic Guidelines (Therapeutic Guidelines Limited, 2019) and the Australian Asthma Handbook (Australia NAC, 2019).

Adherence Calculated *via* Pharmacy Dispensing Data

A complete 12-months pharmacy dispensing history was either collected electronically or manually for each patient. Number of days with medication available was based on the date of medication supply, the number of doses supplied and the prescribed dosage. If no dosage information was provided, the last available instructions for the prescribed medicine was carried forward; if no prior instructions were provided, the standard dose was assumed. In cases where a dose range was prescribed (e.g., 1-2 puffs), the mean dosage was used in calculations.

Adherence Calculated Using Combined Claims Records and Pharmacy Dispensing Data

The number of days with medication available was based on the date of dispensing, the number of doses supplied and the dose instructions. The medication supply dates were based on claims records, and prescribed dosage information was extracted from pharmacy dispensing data. If no dosage information was provided, the last available instruction for the prescribed medication was carried forward. If no instructions were available, the standard dose was assumed.

The analysis spanned all the patients' asthma controller medicines (Global Initiative for Asthma, 2020). Anatomical therapeutic chemical codes, PBS codes and standard daily doses are available in the supplementary material.

Common assumptions in the PDC calculations include: 1) the claims records were complete and accurate 2) dosage remained consistent for the medication dispensed, 3) the purchased medicine(s) was used for the person intended 4) medication coverage (i.e., the availability of the medication), was a proxy for taking the medicine, 5) in cases when a subsequent supply was granted prior to the exhaustion of a previous supply, supply was adjusted so that the prescription start date became the date after the previous refill had ended.

CLASSIFYING PATIENTS AS SINGLE-OR MULTIPLE-PHARMACY USERS

Adherence estimates were calculated using the aforementioned three approaches for the total cohort and then for patient subgroups based on evidence of multiple or single pharmacy use. A patient was considered a multiple-pharmacy user if there was evidence of collecting their asthma controller medicines from more than one pharmacy in the trial period. Specific pharmacies could not be identified in the claims data, therefore discrepancies in pharmacy dispensing data and claims data over the 12-month period were indicative of multiple-pharmacy use. When medication was dispensed from a pharmacy not in the study, these data would be recorded in the claims data but not in the pharmacy dispensing data. Patients who collected their asthma controller medicines from only one pharmacy were considered single pharmacy users. For single pharmacy users all records in the claims data

TABLE 1 | Contents, strengths, and limitations of medication data sources utilized.

Data source	Contents	Strengths	Limitations
Claims Records	Date of medication prescribing Date of medication supply PBS[a] item code Medication name Medication strength Quantity supplied Drug formulation	Complete record of all PBS[a] subsidized medicines, within a set time frame, that have been collected by patients from all pharmacies in Australia	Prescribed dosage not included. Only includes supplied medications with no record of unfilled prescriptions
Pharmacy dispensing data	Date of medication supply PBS[a] item code Medication name Medication strength Quantity supplied Drug formulation Prescribed dosage Prescriber details	Records all medicines collected, within a set time frame, by patients from a particular pharmacy including the prescribed dosage instructions	Site specific. Prescriptions collected from other pharmacies are not recorded. Only includes supplied medications with no record of unfilled prescriptions

[a]*Notes: The Pharmaceutical Benefits Scheme (PBS) is an Australian Government initiative that subsidizes prescription medicines for Australian residents (Australian Government Department of Health, 2021). Any medication dispensed through the PBS, is recorded in a central database upon submission for reimbursement and can be linked to a patient via their unique Medicare ID. PBS medicines are subject to a patient co-payment to a threshold amount based on patient concessional status. This dataset includes medicines both below and above this threshold (excluding items dispensed as "private" or those not on the PBS List).*

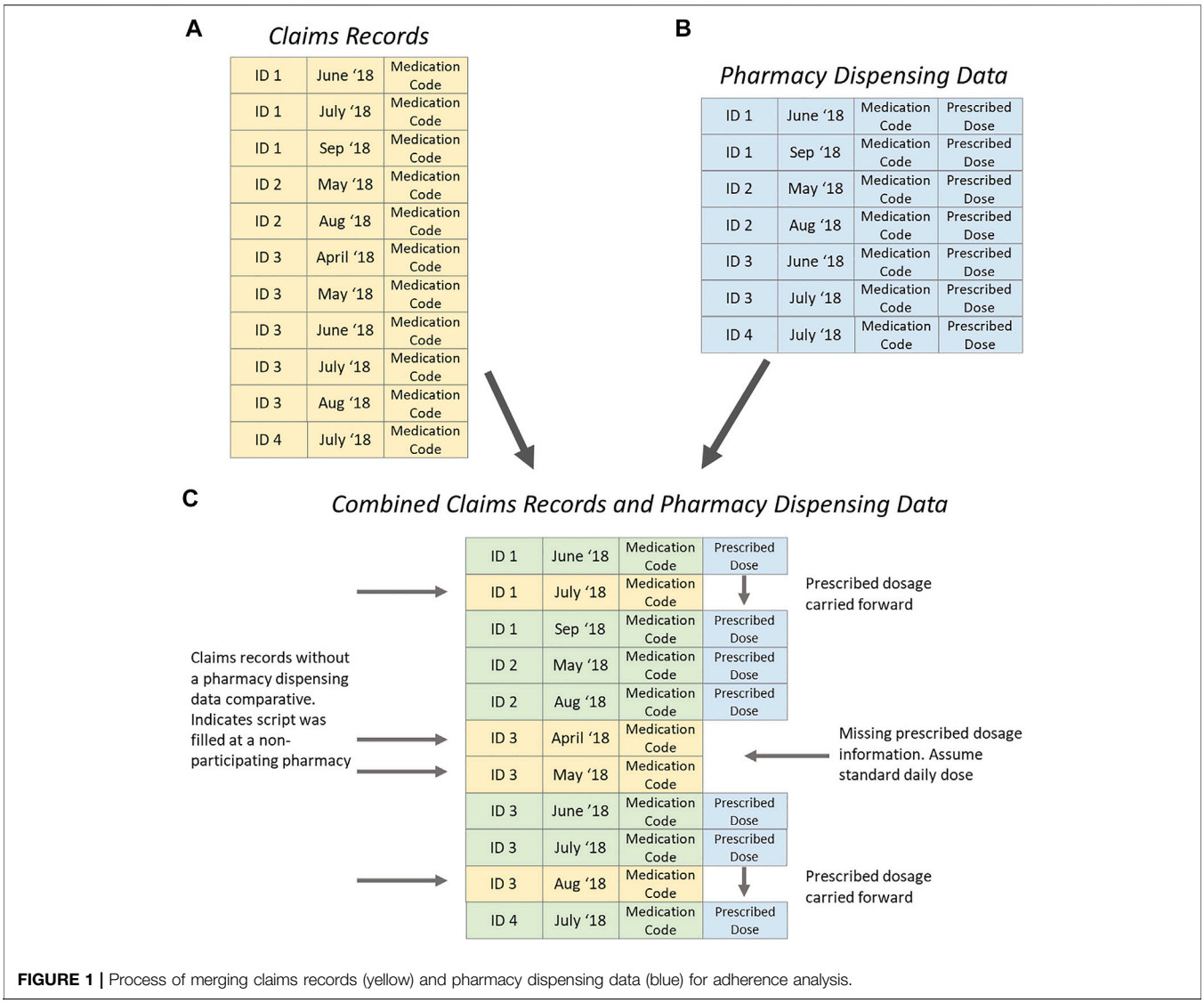


FIGURE 1 | Process of merging claims records (yellow) and pharmacy dispensing data (blue) for adherence analysis.

matched pharmacy dispensing data for medication and date collected.

An additional subgroup analysis was conducted to compare patient demographic factors and clinical measures between patients who had collected asthma controller medicines from a single pharmacy versus multiple pharmacies.

PATIENT CHARACTERISTICS

Patient demographic data included self-reported age, gender, work status, education status, smoking status, allergic rhinitis status and asthma history information including age of asthma onset, whether the patient had a lung function test and whether the patient had an asthma-related emergency presentation and/or hospital admission in the 12 months prior to the trial. Clinical measures compared included baseline asthma control as assessed *via* the ACQ (Juniper et al., 1999), quality of life *via* the Impact of Asthma on Quality of Life Questionnaire (IAQLQ) (Marks et al., 1992), and allergic rhinitis control *via* the Rhinitis Control Assessment Test (RCAT) (Schatz et al., 2010; Meltzer et al., 2013).

DATA ANALYSIS

The claims records contained all pharmaceutical claims made for each patient throughout the 12 months preceding entry to the trial (**Figure 1A**). Pharmacy dispensing data included all asthma controller medicines dispensed at a particular pharmacy as well as the prescribed dosage for each patient (**Figure 1B**). These data sources were linked by Patient (ID) and dispensing data (date). **Figure 1C** illustrates the data scenarios. Patient ID 1 attended multiple pharmacies, when

TABLE 2 | Baseline patient characteristics based on pharmacy use.

	Single pharmacy users (*n* = 195)	Multiple pharmacy users (*n* = 94)	Total (*n* = 289)	Absolute standardized effect size
Pharmacy state				0.277
New South Wales	133/195 (68.2%)	75/94 (79.8%)	208/289 (72.0%)	
Tasmania	23/195 (11.8%)	7/94 (7.4%)	30/289 (10.4%)	
Western Australia	39/195 (20.0%)	12/94 (12.8%)	51/289 (17.6%)	
Pharmacy remoteness[a]				0.047
Highly accessible	127/195 (65.1%)	59/94 (62.8%)	186/289 (64.4%)	
Accessible	49/195 (25.1%)	25/94 (26.6%)	74/289 (25.6%)	
Moderately accessible, remote, very remote	19/195 (9.7%)	10/94 (10.6%)	29/289 (10.0%)	
Age (years)				0.086
18–55	85/195 (43.6%)	45/94 (47.9%)	130/289 (45.0%)	
>55	110/195 (56.4%)	49/94 (52.1%)	159/289 (55.0%)	
Female	141/195 (72.3%)	68/94 (72.3%)	209/289 (72.3%)	0.001
Work Status				0.414
Full-time employed	41/195 (21.0%)	22/94 (23.4%)	63/289 (21.8%)	
Home duties	15/195 (7.7%)	11/94 (11.7%)	26/289 (9.0%)	
Part time or casually employed	48/195 (24.6%)	13/94 (13.8%)	61/289 (21.1%)	
Retired/pensioner	62/195 (31.8%)	41/94 (43.6%)	103/289 (35.6%)	
Other	29/195 (14.9%)	7/94 (7.4%)	36/289 (12.5%)	
Education				0.190
High school education or below	101/195 (51.8%)	50/94 (53.2%)	151/289 (52.2%)	
Tertiary non-university	54/195 (27.7%)	20/94 (21.3%)	74/289 (25.6%)	
University or higher	40/195 (20.5%)	24/94 (25.5%)	64/289 (22.1%)	
Self-reported age of asthma onset (years)				0.403
0–5	34/195 (17.4%)	32/94 (34.0%)	66/289 (22.8%)	
6–15	42/195 (21.5%)	17/94 (18.1%)	59/289 (20.4%)	
16–34	55/195 (28.2%)	20/94 (21.3%)	75/289 (26.0%)	
35–55	36/195 (18.5%)	15/94 (16.0%)	51/289 (17.6%)	
>55	28/195 (14.4%)	10/94 (10.6%)	38/289 (13.1%)	
Self-reported lung function test				0.173
<12 months ago	58/195 (29.7%)	26/94 (27.7%)	84/289 (29.1%)	
≥12 months ago	81/195 (41.5%)	47/94 (50.0%)	128/289 (44.3%)	
Never	56/195 (28.7%)	21/94 (22.3%)	77/289 (26.6%)	
Smoker	30/195 (15.4%)	12/94 (12.8%)	42/289 (14.5%)	0.075
Self-reported allergic rhinitis	141/195 (72.3%)	73/94 (77.7%)	214/289 (74.0%)	0.124
Emergency Department presentation in the last 12 months (Yes)	48/195 (24.6%)	28/94 (29.8%)	76/289 (26.3%)	0.116
Hospital admission in the last 12 months (Yes)	26/195 (13.3%)	22/94 (23.4%)	48/289 (16.6%)	0.262
ACQ score[b] Median (Q1; Q3)	2.2 (1.7; 3.0)	2.2 (1.8; 3.0)	2.2 (1.7; 3.0)	0.075
IAQLQ score[c] Median (Q1; Q3)	3.1 (1.8; 4.8)	3.1 (2.0; 5.0)	3.1 (1.8; 4.9)	0.107
RCAT score[d] Median (Q1; Q3)	20.0 (16.0; 25.0)	21.0 (17.0; 24.0)	20.0 (16.0; 25.0)	0.098

Note: Absolute standardized differences were used to compare subgroups. Values range from 0 to 1, with a higher number indicating a larger difference between the two subgroups.
[a]Participating pharmacies were identified as either "highly accessible" (PhARIA Category 1), "accessible" (PhARIA Categories 2 and 3) or "moderately accessible, remote or very remote" (PhARIA Categories 4, 5 and 6) National Rural Health Alliance, 2011; The University of Adelaide, 2019a; The University of Adelaide, 2019b
[b]Asthma Control Questionnaire (ACQ) score lies between 0 (totally controlled) and 6 (extremely poorly controlled). A score of 1.5 or greater is considered an indication of poorly controlled asthma Juniper et al., 2006.
[c]Impact of Asthma on Quality of Life Questionnaire (IAQLQ) scores lie between 0 and 10. Higher scores represent a greater impact of asthma on quality of life Marks et al., 1992.
[d]Rhinitis Control Assessment Test (RCAT) scores lie between 6 and 30. The lower the score, the more severe the allergic rhinitis; the higher the score, the less severe the allergic rhinitis. Patients scoring ≤21 are considered clinically "symptom uncontrolled"; those scoring >21 are considered "symptom controlled" Meltzer et al., 2013.

the pharmacy was not in the study, the previously recorded prescribing dose was carried forward. Patient ID 2 attended only one pharmacy during the study, and all dosage information was available. Patient ID 3 attended multiple pharmacies; the first dispensing during the study period was not at a participating pharmacy, so no prescribed dosage was available and standard daily dose was assumed. Later in the study when Patient ID 3 attended a pharmacy not in the study, the prescribed dosage was carried forward from a previous dispensing.

The additional information obtained by including the patients' prescribed dose in the PDC calculations was quantified by the difference between the PDC calculated *via* claims records and the PDC calculated *via* the combined claims records and pharmacy dispensing data. A secondary analysis was also performed to identify if the results achieved using PDC scores were consistent when the commonly used binary definition of adherence is used. A patient is considered adherent if their PDC score ≥80%. (Karve et al., 2009; Raebel et al., 2013) Standard summary

TABLE 3 | Patient adherence.

Data source	Single-pharmacy users (n = 195)[a] Mean PDC (SD)	Multiple-pharmacy users (n = 94)[a] Mean PDC (SD)	Total (n = 289)[a] Mean PDC (SD)	Mean difference between the PDCs for single- and multiple-pharmacy users (95% CI) (unpaired t-test)
Pharmacy dispensing data	45.6 (31.5)	35.2 (31.4)	42.2 (31.8)	10.4% (2.6%–18.1%) p = 0.009[a]
Claims records	50.7 (33.3)	67.2 (28.4)	56.1 (32.6)	16.4% (9.0%–23.9%) p < 0.001[a]
Combined claims records and pharmacy dispensing data	45.6 (31.5)	63.9 (29.5)	51.5 (31.9)	18.3% (10.8%–25.7%) p < 0.001[a]
Mean difference between PDC calculated based on pharmacy dispensing data and claims data alone (95% CI) (paired t-test)	5.1% (3.0%–7.3%) p < 0.001[a]	32.0% (27.1%–36.8%) p < 0.001[a]	13.9% (11.3%–16.4%) p <0.001[a]	—

[a]*PDC refers to the Proportion of Days Covered by at least one controller medicine (Raebel et al., 2013).*

statistics were used throughout, including measures of proportions, measures of central tendency (median and mean) and dispersion (the interquartile range (IQR) and standard deviation (SD). Absolute standardized effect sizes (SES) were used to compare groups with respect to cohort characteristics (range 0–1, higher number indicating a larger difference between the two subgroups). Effect sizes and confidence intervals as well as Student's t-tests, both paired and unpaired, and the non-parametric Wilcoxon Rank Sum (WRS) tests were used to compare means and differences of medication adherence measures.

The analysis was performed using both SAS version 9.4, SAS Enterprise Guide 7.1 and R version 3.6.2 (R Core Team, 2018) including R packages *ggplot2* (Wickham, 2016) and *ggridges* (Wilke, 2021). All available demographic and clinical measures were used without imputation.

RESULTS

Patients

Seventy-six percent (n = 289) of the total PTP-ARC trial cohort were included in the analysis. Fifteen percent (n = 57) of the total cohort were excluded as they did not collect an asthma controller medication in the 12 months preceding recruitment, while 9% (n = 35) did not consent to their claim's records being accessed. Single-pharmacy users comprised 67% (n = 195) of the included patients.

Most patients were from NSW (72%), resided in metropolitan areas (64%), and were female (72%), 56 years of age or greater (55%), non-smokers (85%), self-reported having allergic rhinitis (74%) and self-reported a diagnosis of asthma prior to the age of 35 years (68%). All patients had poorly controlled asthma with the cohort mean ACQ score being 2.5 (**Table 2**).

Table 2 presents the absolute standardized differences between multiple pharmacy users and single pharmacy users when subgroups were compared. Single-pharmacy users were comparable to multiple-pharmacy users in most characteristics; however, there were differences with respect to work status and reported age of asthma onset. A higher proportion of multiple-pharmacy users were retired or pensioners (SES = 0.414, percentage retired/pensioner 44% compared to 32%), and the reported age of asthma onset for multiple pharmacy users was younger (SES = 0.403, percentage between 0 and 5 years 34% compared to 17%) compared to single pharmacy users (**Table 2**).

Adherence

The mean PDC estimate for the total cohort using pharmacy dispensing data alone was 42% (SD = 31.8%). This increased significantly to 56% (SD = 32.6%) when claims records were the only source used and to 52% (SD = 31.9%) when combining claims records and the prescribed dosage from pharmacy dispensing data (**Table 3**). The mean difference between the PDC calculated *via* claims records and the PDC calculated *via* the combined claims records and pharmacy dispensing data was 5%, with a standard deviation of 13.7% (Q1 = 0%, Q3 = 8.2%, p-value <0.001, WRS test), indicating a significant finding.

Patients collecting asthma medicines from a single pharmacy had a PDC of 46% (SD = 31.5%) calculated using the pharmacy dispensing data, which increased significantly to 51% (SD = 33.3%) when using claims records alone. When these two sources were compared, the PDC estimate from claims records was equivalent to the PDC calculated using pharmacy dispensing data alone, as no additional information was gained from the claim's records (**Table 3**).

Patients collecting asthma medicines from multiple pharmacies had a PDC estimate of 35% (SD = 31.4%) in analysis of pharmacy dispensing data alone, and 67% (SD = 29.5%) using claims records alone. There was a significant difference in PDC estimates between pharmacy dispensing data and the claims records of 32% (SD = 23.7%) (p-value < 0.001) (**Table 3**). When data sources were combined and adjustments to PDC were made based on the patient prescribed dose (**Figure 1**), the mean PDC reduced to 64% (SD = 29.5%).

Using combined data sources, single-pharmacy users were found to have a significantly lower adherence

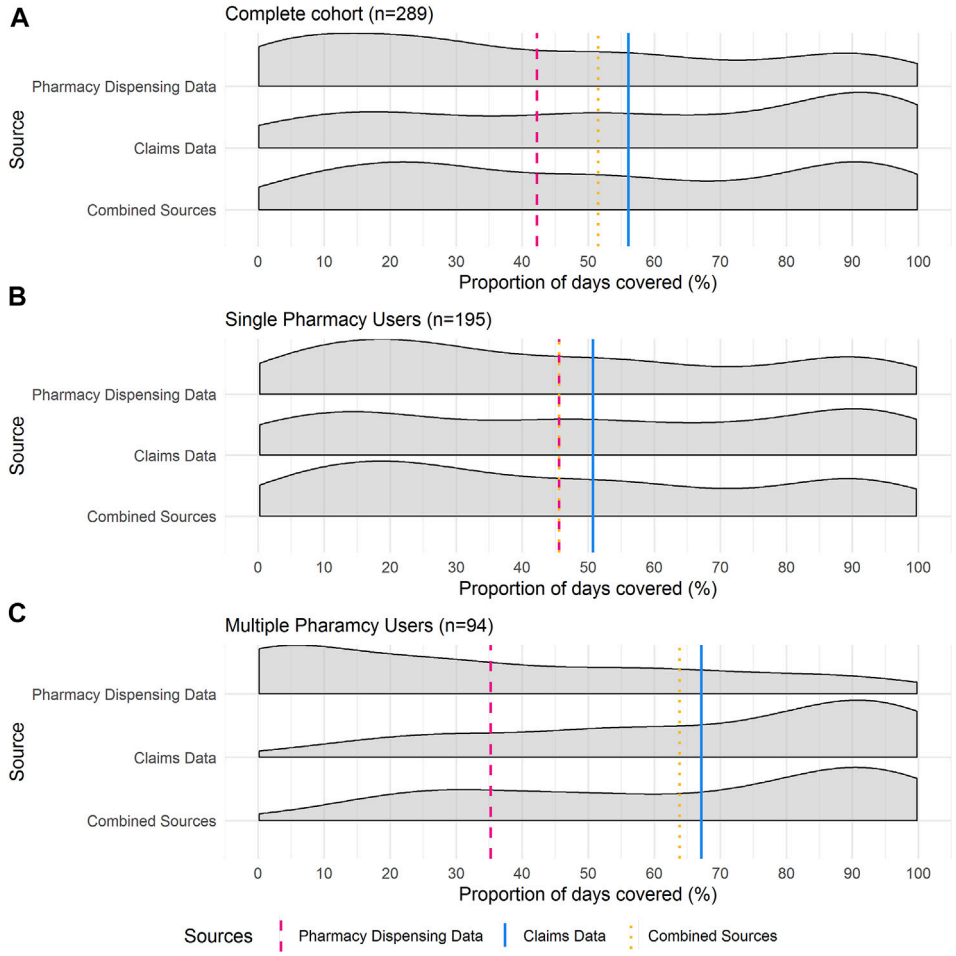


FIGURE 2 | Proportion of Days Covered (PDC) Density curves for **(A)** total cohort (*n* = 289), **(B)** single-pharmacy users (*n* = 195) and **(C)** multiple-pharmacy users (*n* = 94). Vertical lines are representative of mean PDC for each data source. These distribution plots illustrate the consistently larger PDC estimates calculated *via* claims records and the relative closeness in PDC estimates between the claim's records and the combined claims records and pharmacy dispensing data.

estimate than multiple-pharmacy users (18%, 95%CI 11%–26%, $p < 0.001$).

Density plots in **Figure 2** show the distribution of the patients' PDC for the investigated 12-month period by data source and pharmacy use. The distribution of the complete cohort is presented in **Figure 2A** and comprises both single- and multiple-pharmacy users.

When pharmacy dispensing data were considered, a higher proportion of single-pharmacy users had a lower PDC compared to when claims records were used to calculate PDC (**Figure 2B**).

The pharmacy dispensing data for multiple pharmacy users was positively skewed, with a large proportion of patients having lower PDC estimates. Conversely, the distribution of the PDC calculated by claims records was negatively skewed, with most patients having a PDC > 80% (**Figure 2C**).

These distributions highlight the differences in the mean PDC values based on the different data sources. They illustrate the consistently larger PDC estimates calculated *via* claims records and the relative closeness in PDC estimates between the claim's records and the combined claims records and pharmacy dispensing data.

The distributions of change in PDC estimates between claims records and combined claims records and pharmacy dispensing data are shown in **Figure 3**. All three cohorts are negatively skewed with a center around zero. This indicates that the standard daily dose assumption used when PDC estimates are calculated using claims records alone underestimate the PDC compared to when estimates are calculated using the combined claims records and pharmacy dispensing data.

For the complete cohort, the mean difference between the PDC calculated *via* claims records and the PDC calculated *via* the combined claims records and pharmacy dispensing data was −5%, (SD = 13.7) with an interquartile range of 8.2% (Q1 = −8.2%, Q3 = 0%, p-value < 0.001, WRS test). This difference indicates that the PDC calculated using the prescription dose information was lower than when standard dose was assumed. The standard daily dose assumption overestimated the PDC coverage by 4.6%. For single-pharmacy users, the mean

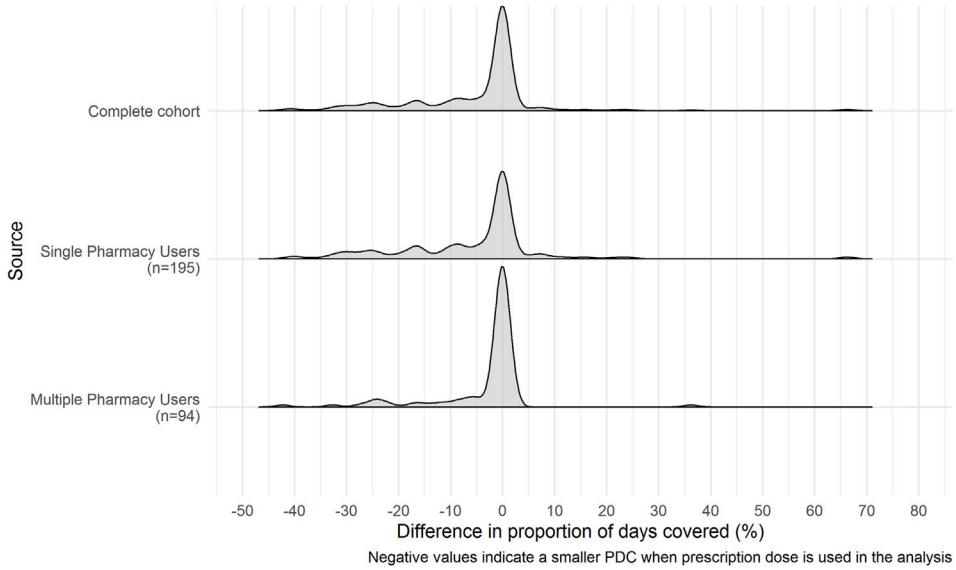


FIGURE 3 | Distribution of differences in Proportion of Days Covered estimates between claims records alone and combined claims records and pharmacy dispensing data. Negative values indicate a lower PDC when patients prescribed dose is included in the analysis instead of the standard dose assumption. The differences between the PDC estimates based on patients prescribed dose versus the standard dose assumption have a skewed distribution. Therefore, it is likely that greater dose variability amongst some asthma patients within the cohort may have contributed to this finding.

change in PDC was -5% (SD = 15.3%), with an IQR of 11.1% (Q1 = −11.1%, Q3 = 0%, p-value < 0.001, WRS test), and for multiple pharmacy users, the mean change in PDC was −3% (SD = 9.4), with an IQR of 0.4% (Q1 = −0.4%, Q3 = 0%, p-value <0.001, WRS test).

All PDC findings were consistent when the sensitivity analysis was performed based on the binary measure of the proportion of patient's adherent (PDC ≥ 80%) (see **Supplementary Material**).

DISCUSSION

A novel assessment of patient adherence to asthma controller therapy was conducted by combining patient-specific prescribed dosage data found in pharmacy dispensing data with routinely collected claims records to determine the added value of using both sources of data. PDC estimates based on pharmacy dispensing data alone or combined claims records and pharmacy dispensing data were significantly lower than estimates based on claims records alone, indicating that perhaps standard daily dose is not a robust proxy for prescribed dosage to inhaled respiratory devices in adherence approximations. However, PDC estimates based on combined pharmacy dispensing and claims records or claims records alone were significantly higher than estimates based on pharmacy dispensing data alone for the total cohort and more noticeably for multiple pharmacy users. Thus, the use of claims records over site-specific pharmacy dispensing data and the use of patient specific prescribed dosage adds value to clinical assessments and provides a clearer indication of a patient's medication adherence.

There was a significant difference when utilizing patient-specific prescribed doses sourced from pharmacy dispensing data over the standard dose assumption. This challenges the methodology and assumptions used in prior claims-based pharmacoepidemiologic research. However, whether these differences are clinically significant in practice and reproducible in other therapeutic areas requires further research. It should be noted that the differences between the PDC estimates based on patients prescribed dose versus the standard dose assumption have a skewed distribution. Therefore, it is likely that greater dose variability amongst some asthma patients within the cohort may have contributed to this finding. Future exploration would be interesting to determine why this is the case for some patients and how these patients and their medication management differs from the majority of the cohort.

Adherence was poor amongst this cohort, irrespective of the data source, and across all subgroups. Low levels of adherence are consistent with the literature (Price et al., 2014; Price et al., 2015; Reddel et al., 2015). Moreover, the single-pharmacy users had considerably lower levels of adherence than their multiple-pharmacy user counterparts. This may seem counter intuitive and in direct contrast to available literature which supports association of multiple pharmacy use with lower medication adherence and increased risk of drug-drug interactions (Taitel et al., 2012). The difference between our investigation and those published may reflect the different therapeutic areas and medicines being investigated or international differences in the patient and pharmacy cohorts. Our results suggest that,

suboptimal adherence remains a significant issue that requires addressing before a more beneficial clinical trajectory for asthma patients can be realized to reduce the associated health economic burden (Cutler et al., 2018). There is opportunity for pharmacists to improve upon this low adherence by using targeted interventions when regular patients collect medications.

Pharmacy dispensing data consistently underestimated patient adherence to therapy particularly for multiple-pharmacy users. There is a disconnect between the data that pharmacists can access and the data that can more fully inform pharmacists about a patient's adherence. However, routinely collected claims records could complement site-specific pharmacy dispensing data and thus increase a pharmacist's assessment of a patient's medication adherence. This is likely to be of benefit in many therapeutic areas. Expanding the pharmacist's access to data allows them to make clinical judgements with greater clarity and to offer better patient specific care. Furthermore, the use of claims based records in place of pharmacy-based data will improve sensitivity of adherence software programs currently used in community pharmacies to focus on patients with adherence issues (GuildLink, 2021).

The advantages of centralized and accessible registry data are apparent and recognized internationally (Wright and Twigg, 2016; Nelson et al., 2017; Jackson and Peterson, 2019; The Organisation for Economic Co-operation and Development, 2019; The Commonwealth Fund, 2021). These findings offer another clinical incentive for countries still operating with fragmented reporting networks to work towards the creation of a central data system which would be better able to serve patients and assist in real time clinical decision making. Within community pharmacy, the use of electronic health record data has the ability to elevate current standards of practice by providing a holistic view of patient management and assisting in reducing medication misadventure (Wright and Twigg, 2016; Jackson and Peterson, 2019). For example, in Australia, the increasing integration of patient electronic health records (My Health Records) (Australian government Australian Digital Health Agency, 2019) into primary care and community pharmacy allows pharmacists access to complete claims records for consenting patients under their care (Australia TPSo, 2019). However, research exploring application of these opportunities within community pharmacy practice is limited. With regard to adherence, the use of centralized data is centered on monitoring trends in medicine consumption and spending at national and cohort levels, rather than how such information could be used on a patient-by-patient basis to improve health outcomes for individuals (The Organisation for Economic Co-operation and Development, 2019; The Commonwealth Fund, 2021). Further work is needed to realize the full utility of centralized datasets in community pharmacy practice and automated systems and specific frameworks developed to facilitate this. This will allow integration with workflow and software to optimize health benefits and best safeguards patient privacy (Wright and Twigg, 2016; Kosari et al., 2020).

Our findings prompt reflection on pre/post adherence intervention-based studies using pharmacy dispensing data alone as an outcome measure (Armour et al., 2008; Taitel et al., 2012; Pringle et al., 2014; Stewart et al., 2014). Not only was there the possibility that adherence may have been underestimated, limited by data available at the time, it would also be difficult to differentiate between improved adherence based on the intervention in question and improved loyalty to a pharmacy, or confounding between these factors and a patient's adherence. Collection of medicines from a single pharmacy providing a better quality of care would improve the apparent adherence estimate over time compared to where a patient continued to collect medications from multiple pharmacies based on convenience.

Allowing access to routinely collected data may also benefit general practitioners. Within general practice, knowledge of a patient's adherence can assist by breaking the cycle of uncontrolled asthma symptoms, review and therapy escalation that ensues if suboptimal adherence is left undetected (Serhal et al., 2020). Clinicians would be able to differentiate poor asthma control as a result of suboptimal adherence from poor therapeutic response to medicines. The utility of marrying two data sources would also prove useful within a general practice setting. Prescribing data combined with claims records would overcome practitioner limitations when it comes to monitoring for primary non-adherence: whether a patient is having their prescribed medicines dispensed (Tibble et al., 2020) or "doctor shopping" practices that could lead to the overestimation or underestimation of a patient's adherence. This methodology could also be applied to other therapeutic areas in practice and in future research to enrich patient chronic care management and offer positive implications for drugs of addiction or abuse potential i.e., real time monitoring of patient opioid use and oversight of doctor and pharmacy shopping practices.

In the future, there could be benefit in a simple multiplication factor being created *via* analysis of claims records and used as clinical tool for pharmacists to approximate patient adherence based on pharmacy data. However, this would require repeated investigations and validation, and may differ depending on the therapeutic area.

Strengths and Limitations

To the best of our knowledge this is the first study to have access to a linked set of pharmacy dispensing data and pharmaceutical claims records for a cohort of patients. Additionally, it is the first time these data sources have been combined to create a novel measure of adherence that can be compared to traditionally used methods.

Measures of adherence disclosed in this manuscript are proxy measures of adherence. These measures represent medicine acquisition, but not necessarily medicine usage.

Adherence estimates were based on any asthma controller medicines collected within a set period, which assumes patients had not changed their behaviors prior to or during the study, i.e., there was no stockpiling of medicines by patients. However, the same rule applied to both data sources, and as this study focuses on comparing adherence rates and not the rates

themselves, it is expected this effect would have minimal impact on the findings.

Thirty-three percent of patients collected their asthma medications from multiple pharmacies, despite an inclusion criterion that patients should be regular patrons of the pharmacy in which they were recruited. Despite this anomaly, this 33% figure is consistent with available literature (Look and Mott, 2003; Marcum et al., 2014; Marcum et al., 2017; The Pharmacy Guild of Australia, 2018; Pearson DDL, 2021).

CONCLUSION

Access to routinely collected claims records and patient prescribed dosage increases clinical acuity of patient adherence estimates to asthma controller medicines and is a valuable resource for healthcare professionals. Secure accessibility of such data at the patient-pharmacist or patient-GP interface may allow real-time intervention and assist in decision making across numerous therapeutic areas.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because Pharmaceutical Benefits Scheme data is subject to approval by Services Australia prior to distribution. Requests to access the datasets should be directed to sarah.serhal@sydney.edu.au.

ETHICS STATEMENT

This study involved human participants and was reviewed and approved by the University of Sydney. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization: SSe, AC, CA, and LBi; Data Curation: AC, SSh, and SSe; Formal Analysis: AC Funding acquisition: CA and LBi; Investigation: SSe and AC; Methodology: AC and SSe; Project administration: AC and SSe; Supervision: AC, CA, and LBi; Visualization: AC; Writing original draft: SSe and AC; Writing review and editing: SSe, AC, CA, IK, LE, BS, SB-A, BB, LBe, and LBi.

FUNDING

This work was supported by the Commonwealth of Australia as represented by the Department of Health *via* the Sixth Community Pharmacy Agreement (6CPA).

ACKNOWLEDGMENTS

Services Australia (formerly the Department of Human Services) is acknowledged for supplying the Pharmaceutical Benefits Scheme (PBS) information.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.869162/full#supplementary-material

REFERENCES

American Pharmacist Association (2020). Measuring Adherence. Available from: https://www.pharmacist.com/measuring-adherence (Accessed 06 18, 2020).

Amin, S., Soliman, M., McIvor, A., Cave, A., and Cabrera, C. (2020). Usage Patterns of Short-Acting β2-Agonists and Inhaled Corticosteroids in Asthma: A Targeted Literature Review. *J. Allergy Clin. Immunol. Pract.* 8 (8), 2556–e8. e8. doi:10.1016/j.jaip.2020.03.013

Armour, C., Bosnic-Anticevich, S., Brillant, M., Burton, D., Emmerton, L., Krass, I., et al. (2007). Pharmacy Asthma Care Program (PACP) Improves Outcomes for Patients in the Community. *Thorax* 62 (6), 496–502. doi:10.1136/thx.2006.064709

Armour, C. L., Smith, L., and Krass, I. (2008). Community Pharmacy, Disease State Management, and Adherence to Medication. *Dis. Manag. Health Outcomes* 16 (4), 245–254. doi:10.2165/00115677-200816040-00005

Australia Nac (2019). Australian Asthma Handbook - the National Guidelines for Health Professionals. Available from: http://www.asthmahandbook.org.au/diagnosis (Accessed 02 26, 2020).

Australia TPSo (2019). My Health Record Guidelines for Pharmacists. Available from: https://www.psa.org.au/wp-content/uploads/2019/09/MHR-Guidelines-for-Pharmacists.pdf (Accessed 112, 2020).

Australian government Australian Digital Health Agency (2019). What Is My Health Record? Available from: https://www.myhealthrecord.gov.au/for-healthcare-professionals/what-is-my-health-record (Accessed July 7th, 2021).

Australian Government Department of Health (2021). About the PBS. Available from: https://www.pbs.gov.au/info/about-the-pbs (Accessed July 7th, 2021).

Australian Institute of Health and Welfare (2018). *Using PBS and MBS Data to Report on the Treatment and Management of Chronic Respiratory Conditions 2016–17*. Available from: https://www.aihw.gov.au/getmedia/ae99bd43-684d-44dd-b7b1-3ef8f700d817/aihw-acm-37.pdf.aspx?inline=true (Accessed 04 01, 2020).

Australian Medicines Handbook (2020). Australian Medicines Handbook Pty Ltd. Available from: https://amhonline.amh.net.au/(Accessed July 7.

Australian New Zealand Clinical Trials Registry (2018). Trial Review - Pharmacy Trial Program (PTP)- Getting Asthma under Control Using the Skills of the Community Pharmacist. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374558&isReview=true (Accessed December 9th, 2019).

Chan, A. H., Reddel, H. K., Apter, A., Eakin, M., Riekert, K., and Foster, J. M. (2013). Adherence Monitoring and E-Health: How Clinicians and Researchers Can Use Technology to Promote Inhaler Adherence for Asthma. *J. Allergy Clin. Immunol. Pract.* 1 (5), 446–454. doi:10.1016/j.jaip.2013.06.015

Cutler, R. L., Fernandez-Llimos, F., Frommer, M., Benrimoj, C., and Garcia-Cardenas, V. (2018). Economic Impact of Medication Non-adherence by

Disease Groups: a Systematic Review. *BMJ Open* 8 (1), e016982. doi:10.1136/bmjopen-2017-016982

DiSantostefano, R. L., Yeakey, A. M., Raphiou, I., and Stempel, D. A. (2013). An Evaluation of Asthma Medication Utilization for Risk Evaluation and Mitigation Strategies (REMS) in the United States: 2005-2011. *J. Asthma* 50 (7), 776–782. doi:10.3109/02770903.2013.803116

Eduardo Sabaté (2003). *Adherence to Long Term Therapies - Evidence for Action Geneva Switzerland*. Geneva: World Health Organization. Available from: https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf (Accessed 2112, 2021).

Elliott, R. A., Pharmacist, C., and Health, A. (2006). Problems with Medication Use in the Elderly: An Australian Perspective. *J. Pharm. Pract. Res.* 36, 58–66. doi:10.1002/j.2055-2335.2006.tb00889.x

Global Initiative for Asthma (2020). *Global Strategy for Asthma Management and Prevention - Updated 2020*. Available from: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf (Accessed 04 24, 2020).

Golay, A. (2011). Pharmacoeconomic Aspects of Poor Adherence: Can Better Adherence Reduce Healthcare Costs? *J. Med. Econ.* 14 (5), 594–608. doi:10.3111/13696998.2011.597808

GuildLink (2021). Patient Adherence Programs. Available from: http://www.guildlink.com.au/guildcare/products1/guildcare-programs/patient-adherence-programs/(Accessed 1512, 2021).

Haynes, R. B., Ackloo, E., Sahota, N., McDonald, H. P., and Yao, X. (2008). Interventions for Enhancing Medication Adherence. *Cochrane Database Syst. Rev.* (2), Cd000011. doi:10.1002/14651858.CD000011.pub3

Hull, S. A., McKibben, S., Homer, K., Taylor, S. J., Pike, K., and Griffiths, C. (2016). Asthma Prescribing, Ethnicity and Risk of Hospital Admission: an Analysis of 35,864 Linked Primary and Secondary Care Records in East London. *NPJ Prim. Care Respir. Med.* 26, 16049. doi:10.1038/npjpcrm.2016.49

Jackson, S., and Peterson, G. (2019). My Health Record: a Community Pharmacy Perspective. *Aust. Prescr* 42 (2), 46–47. doi:10.18773/austprescr.2019.009

Juniper, E. F., Bousquet, J., Abetz, L., and Bateman, E. D. (2006). Identifying 'well-Controlled' and 'Not Well-Controlled' Asthma Using the Asthma Control Questionnaire. *Respir. Med.* 100 (4), 616–621. doi:10.1016/j.rmed.2005.08.012

Juniper, E. F., O'Byrne, P. M., Guyatt, G. H., Ferrie, Pj., and King, Dr. (1999). Development and Validation of a Questionnaire to Measure Asthma Control. *Eur. Respir. J.* 14 (4), 902–907. doi:10.1034/j.1399-3003.1999.14d29.x

Kardas, P., Aguilar-Palacio, I., Almada, M., Cahir, C., Costa, E., Giardini, A., et al. (2020). The Need to Develop Standard Measures of Patient Adherence for Big Data: Viewpoint. *J. Med. Internet Res.* 22 (8), e18150. doi:10.2196/18150

Karve, S., Cleves, M. A., Helm, M., Hudson, T. J., West, D. S., and Martin, B. C. (2009). Good and Poor Adherence: Optimal Cut-point for Adherence Measures Using Administrative Claims Data. *Curr. Med. Res. Opin.* 25 (9), 2303–2310. doi:10.1185/03007990903126833

Kosari, S., Yee, K. C., Mulhall, S., Thomas, J., Jackson, S. L., Peterson, G. M., et al. (2020). Pharmacists' Perspectives on the Use of My Health Record. *Pharmacy (Basel)* 8 (4), 190. doi:10.3390/pharmacy8040190

Lehmann, A., Aslani, P., Ahmed, R., Celio, J., Gauchet, A., Bedouch, P., et al. (2014). Assessing Medication Adherence: Options to Consider. *Int. J. Clin. Pharm.* 36 (1), 55–69. doi:10.1007/s11096-013-9865-x

Linnet, K., Halldórsson, M., Thengilsdóttir, G., Einarsson, Ó. B., Jónsson, K., and Almarsdóttir, A. B. (2012). Primary Non-adherence to Prescribed Medication in General Practice: Lack of Influence of Moderate Increases in Patient Copayment. *Fam. Pract.* 30 (1), 69–75. doi:10.1093/fampra/cms049

Look, K. A., and Mott, D. A. (2003). Multiple Pharmacy Use and Types of Pharmacies Used to Obtain Prescriptions. *J. Am. Pharm. Assoc. (2003)* 53 (6), 601–610. doi:10.1331/JAPhA.2013.13040

Marcum, Z. A., Driessen, J., Thorpe, C. T., Gellad, W. F., and Donohue, J. M. (2014). Effect of Multiple Pharmacy Use on Medication Adherence and Drug-Drug Interactions in Older Adults with Medicare Part D. *J. Am. Geriatr. Soc.* 62 (2), 244–252. doi:10.1111/jgs.12645

Marcum, Z. A., Hanlon, J. T., and Murray, M. D. (2017). Improving Medication Adherence and Health Outcomes in Older Adults: An Evidence-Based Review of Randomized Controlled Trials. *Drugs Aging* 34 (3), 191–201. doi:10.1007/s40266-016-0433-7

Marks, G. B., Dunn, S. M., and Woolcock, A. J. (1992). A Scale for the Measurement of Quality of Life in Adults with Asthma. *J. Clin. Epidemiol.* 45 (5), 461–472. doi:10.1016/0895-4356(92)90095-5

Meltzer, E. O., Schatz, M., Nathan, R., Garris, C., Stanford, R. H., and Kosinski, M. (2013). Reliability, Validity, and Responsiveness of the Rhinitis Control Assessment Test in Patients with Rhinitis. *J. Allergy Clin. Immunol.* 131 (2), 379–386. doi:10.1016/j.jaci.2012.10.022

National Asthma Council Australia (2019). Australian Asthma Handbook | Managing Asthma in Adults. Available from: https://www.asthmahandbook.org.au/management/adults (Accessed February 5.

National Center for Chronic Disease Prevention and Health Promotion (2015). *Calculating Proportion of Days Covered (PDC) for Antihypertensive and Antidiabetic Medications; an Evaluation Guide for Grantees*.

National Collaborating Centre for Primary (2009). *National Institute for Health and Clinical Excellence: Guidance. Medicines Adherence: Involving Patients in Decisions about Prescribed Medicines and Supporting Adherence*. LondonUK: Royal College of General Practitioners.

National Rural Health Alliance (2011). Demography. Available from: https://www.ruralhealth.org.au/book/demography (Accessed 03 08, 2020).

Nelson, S. D., Poikonen, J., Reese, T., El Halta, D., and Weir, C. (2017). The Pharmacist and the EHR. *J. Am. Med. Inform. Assoc.* 24 (1), 193–197. doi:10.1093/jamia/ocw044

Pearson Ddl, R. (2021). *NAB Pharmacy Survey 2021*.

Price, D., David-Wang, A., Cho, S. H., Ho, J. C., Jeong, J. W., Liam, C. K., et al. (2015). Time for a New Language for Asthma Control: Results from REALISE Asia. *J. Asthma Allergy* 8, 93–103. doi:10.2147/JAA.S82633

Price, D., Fletcher, M., and van der Molen, T. (2014). Asthma Control and Management in 8,000 European Patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) Survey. *NPJ Prim. Care Respir. Med.* 24, 14009. doi:10.1038/npjpcrm.2014.9

Pringle, J. L., Boyer, A., Conklin, M. H., McCullough, J. W., and Aldridge, A. (2014). The Pennsylvania Project: Pharmacist Intervention Improved Medication Adherence and Reduced Health Care Costs. *Health Aff. (Millwood)* 33 (8), 1444–1452. doi:10.1377/hlthaff.2013.1398

R Core Team. R (2018). *A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. Available from: https://www.R-project.org/.

Raebel, M. A., Schmittdiel, J., Karter, A. J., Konieczny, J. L., and Steiner, J. F. (2013). Standardizing Terminology and Definitions of Medication Adherence and Persistence in Research Employing Electronic Databases. *Med. Care* 51 (8 Suppl. 3), S11–S21. doi:10.1097/MLR.0b013e31829b1d2a

Reddel, H. K., Sawyer, S. M., Everett, P. W., Flood, P. V., and Peters, M. J. (2015). Asthma Control in Australia: a Cross-Sectional Web-Based Survey in a Nationally Representative Population. *Med. J. Aust.* 202 (9), 492–497. doi:10.5694/mja14.01564

Sansone, R. A., and Sansone, L. A. (2012). Doctor Shopping: a Phenomenon of many Themes. *Innov. Clin. Neurosci.* 9 (11-12), 42–46.

Schatz, M., Meltzer, E. O., Nathan, R., Derebery, M. J., Mintz, M., Stanford, R. H., et al. (2010). Psychometric Validation of the Rhinitis Control Assessment Test: a Brief Patient-Completed Instrument for Evaluating Rhinitis Symptom Control. *Ann. Allergy Asthma Immunol.* 104 (2), 118–124. doi:10.1016/j.anai.2009.11.063

Schneeweiss, S., and Avorn, J. (2005). A Review of Uses of Health Care Utilization Databases for Epidemiologic Research on Therapeutics. *J. Clin. Epidemiol.* 58 (4), 323–337. doi:10.1016/j.jclinepi.2004.10.012

Serhal, S., Saini, B., Bosnic-Anticevich, S., Krass, I., Emmerton, L., Bereznicki, B., et al. (2021). A Targeted Approach to Improve Asthma Control Using Community Pharmacists. *Front. Pharmacol.* 12, 798263. doi:10.3389/fphar.2021.798263

Serhal, S., Saini, B., Bosnic-Anticevich, S., Krass, I., Wilson, F., and Armour, C. (2020). Medication Adherence in a Community Population with Uncontrolled Asthma. *Pharmacy (Basel)* 8 (4). doi:10.3390/pharmacy8040183

Stewart, K., George, J., Mc Namara, K. P., Jackson, S. L., Peterson, G. M., Bereznicki, L. R., et al. (2014). A Multifaceted Pharmacist Intervention to Improve Antihypertensive Adherence: a Cluster-Randomized, Controlled

Trial (HAPPy Trial). *J. Clin. Pharm. Ther.* 39 (5), 527–534. doi:10.1111/jcpt.12185

Taitel, M., Jiang, J., Rudkin, K., Ewing, S., and Duncan, I. (2012). The Impact of Pharmacist Face-To-Face Counseling to Improve Medication Adherence Among Patients Initiating Statin Therapy. *Patient Prefer Adherence* 6, 323–329. doi:10.2147/PPA.S29353

The Commonwealth Fund (2021). What Is the Status of Electronic Health Records? [Available from: https://www.commonwealthfund.org/international-health-policy-center/system-features/what-status-electronic-health-records (Accessed 1012, 2021).

The Organisation for Economic Co-operation and Development (2019). *Using Routinely Collected Data to Inform Pharmaceutical Policies.* [Available from: https://ec.europa.eu/health/sites/default/files/policies/docs/2019_collecteddata_pharmaceuticalpolicies_countrynotes_en.pdf (Accessed 1012, 2021).

The Pharmacy Guild of Australia (2018). *Community Pharmacy 2025 - Market Research Integrated Summary Report*.

The University of Adelaide (2019a). Hugo Centre for Migration and Population Research - Pharmacy ARIA (PHARIA). Available from: https://www.adelaide.edu.au/hugo-centre/services/pharia (Accessed 03 08, 2020).

The University of Adelaide (2019b). Pharmacy ARIA (PhARIA). Available from: https://www.adelaide.edu.au/hugo-centre/services/pharia (Accessed January 16.

Therapeutic Guidelines Limited (2019). eTG Complete. Available from: https://www.tg.org.au (Accessed July 7.

Tibble, H., Lay-Flurrie, J., Sheikh, A., Horne, R., Mizani, M. A., Tsanas, A., et al. (2020). Linkage of Primary Care Prescribing Records and Pharmacy Dispensing Records in the Salford Lung Study: Application in Asthma. *BMC Med. Res. Methodol.* 20 (1), 303. doi:10.1186/s12874-020-01184-8

Torres-Robles, A., Benrimoj, S. I., Gastelurrutia, M. A., Martinez-Martinez, F., Peiro, T., Perez-Escamilla, B., et al. (2021). Effectiveness of a Medication Adherence Management Intervention in a Community Pharmacy Setting: a Cluster Randomised Controlled Trial. *BMJ Qual. Saf.* 31, 105–115. bmjqs-2020-011671. doi:10.1136/bmjqs-2020-011671

Wickham, H. (2016). *ggplot2: Elegant Graphics for Data Analysis*. New YorkNew York: Springer-Verlag.

Wilke, C. O. (2021). *Ggridges: Ridgeline Plots in 'ggplot2'*. R package version 0.5.3. Available from: https://CRAN.R-project.org/package=ggridges.

Wright, D. J., and Twigg, M. J. (2016). Community Pharmacy: an Untapped Patient Data Resource. *Integr. Pharm. Res. Pract.* 5, 19–25. doi:10.2147/IPRP.S83261

Yeaw, J., Benner, J. S., Walt, J. G., Sian, S., and Smith, D. B. (2009). Comparing Adherence and Persistence across 6 Chronic Medication Classes. *J. Manag. Care Pharm.* 15 (9), 728–740. doi:10.18553/jmcp.2009.15.9.728

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 01 April 2022
doi: 10.3389/fphar.2022.850045

Hydralazine Associated With Reduced Therapeutic Phlebotomy Frequency in a Nationwide Cohort Study: Real-World Effectiveness for Drug Repurposing

Wei-Zhi Lin[1], *Chi-Hsiang Chung*[2,3,4], *Chia-Yang Shaiu*[5,6], *Bing-Heng Yang*[5,7]* and *Wu-Chien Chien*[1,2,3,4]*

[1]Graduate Institute of Life Sciences, National Defense Medical Center, Taipei, Taiwan, [2]School of Public Health, National Defense Medical Center, Taipei, Taiwan, [3]Department of Medical Research, Tri-Service General Hospital, Taipei, Taiwan, [4]Taiwanese Injury Prevention and Safety Promotion Association, Taipei, Taiwan, [5]National Defense Medical Center, Graduate Institute of Medical Sciences, Taipei, Taiwan, [6]Fidelity Regulation Therapeutics Inc., Taoyuan, Taiwan, [7]Division of Clinical Pathology, Department of Pathology, Tri-Service General Hospital, Taipei, Taiwan

OPEN ACCESS

Edited by:
Andrea Burden,
ETH Zürich, Switzerland

Reviewed by:
Mohamed A. Yassin,
Hamad Medical Corporation, Qatar
Joung Kyung-In,
Seoul National University, South Korea

***Correspondence:**
Bing-Heng Yang
rodancer0629@gmail.com
Wu-Chien Chien
chienwu@mail.ndmctsgh.edu.tw

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: 07 January 2022
Accepted: 01 March 2022
Published: 01 April 2022

Citation:
Lin W-Z, Chung C-H, Shaiu C-Y, Yang B-H and Chien W-C (2022) Hydralazine Associated With Reduced Therapeutic Phlebotomy Frequency in a Nationwide Cohort Study: Real-World Effectiveness for Drug Repurposing. Front. Pharmacol. 13:850045. doi: 10.3389/fphar.2022.850045

Background: Therapeutic phlebotomy, known as scheduled bloodletting, has been the main method for managing erythrocytosis symptoms and thrombocytosis-associated complications in various blood disorders. One of the major indications for phlebotomy is polycythemia vera (PV). The main goal of current treatment strategies for patients who require phlebotomy is to prevent thrombohemorrhagic complications rather than to prolong survival or lessen the risk of myelofibrotic or leukemic progression. Additional cytoreductive therapy is recommended for high-risk PV, for which the common first-line drug is hydroxyurea. However, recent evidence suggests that phlebotomy may not reduce the risk of thrombosis in patients with PV. Further evidence suggests that patients with PV treated with hydroxyurea who require three or more phlebotomy procedures per year have a higher risk of thrombotic complications.

Methods: We hypothesized that a drug-repurposing strategy of utilizing antineoplastic drugs for patients who require phlebotomy would result in greater benefits than would phlebotomy. The antihypertensive hydralazine and the anticonvulsant valproate, which have both been reported to have antineoplastic activity that mimics cytoreductive agents, were selected as candidates for the drug-repositioning strategy in a retrospective cohort study. We measured the hazard ratios (HR) and the frequencies of phlebotomy in patients with prescriptions for hydralazine or valproate or the two drugs in combination by using data from Taiwan's National Health Insurance Research Database from 2000 to 2015 (n = 1,936,512).

Abbreviations: CCI_R, Charlson comorbidity index without the diseases listed in **Section 2.4**; DDD, defined daily dose; GI hemorrhage, gastrointestinal hemorrhage; HR, hazard ratio; *ICD-9-CM*, *international classification of diseases, 9th revision, clinical modification*; JAK2, Janus kinase 2; NHIRD, national health insurance research database; PV, polycythemia vera.

Results: The HRs of undergoing phlebotomy in groups with hydralazine, valproate, and combination hydralazine–valproate prescriptions were reduced to 0.729 ($p = 0.047$), 0.887 ($p = 0.196$), and 0.621 ($p = 0.022$), respectively. The frequency of undergoing phlebotomy decreased from 2.27 to 1.99, 2.01, and 1.86 per person-year ($p = 0.015$), respectively. However, no significant differences were observed for the hydralazine group or the hydralazine–valproate combination group.

Conclusion: Whether a repurposed drug can serve as a cytoreductive agent for patients who require phlebotomy depends on its risk–benefit balance. We suggest that hydralazine, instead of the hydralazine–valproate combination, is a reasonable alternative for patients who require regular phlebotomy.

Keywords: hydralazine, valproate, therapeutic phlebotomy, cohort study, population-based study, national health insurance database

INTRODUCTION

Polycythemia vera (PV) is a neoplastic marrow disorder characterized by the overproduction of red blood cells that affects up to 2.2 persons per 10,000 individuals (Ma et al., 2008; Arber et al., 2016). Currently, few treatment options exist for PV, and patients face the risk of leukemia transformation and myelofibrotic transformation (Cerquozzi et al., 2017; Landtblom et al., 2018). Patients aged under 60 who have no history of thrombosis are classified as a low-risk population. Such patients receive low-dose aspirin as a front-line treatment to prevent thrombotic complications. Therapeutic phlebotomy is performed if these patients' hematocrit content is higher than 45% (Assi and Baz, 2014; Kim et al., 2021). However, recent evidence suggests that phlebotomy may not reduce the risk of thrombosis in PV (Barbui et al., 2017). Patients aged over 60 years or who have a prior history of thrombosis are classified as a high-risk population. For such patients, the use of hydroxyurea, a chemotherapy drug that inhibits the abnormal proliferation of blood cells (Kim et al., 2021), is recommended. However, some patients cannot tolerate it, and it is also considered to be a risk factor for leukemia transformation or even death (Alvarez-Larran et al., 2012; Cerquozzi et al., 2017). Furthermore, patients with PV treated with hydroxyurea who require three or more phlebotomy procedures per year have a higher risk of thrombotic complications (Alvarez-Larrán et al., 2017). JAK2 and its downstream signal transducer and activator of transcription pathway are known to be abnormally active in PV. This is caused by an increasing JAK2 copy number and a frequently acquired variant, JAK2V617F, which is carried by 95% of those with PV (Campbell et al., 2005; Levine et al., 2005; Scott et al., 2007). Several JAK2 inhibitors, such as fedratinib (Talpaz and Kiladjian, 2021) and ruxolitinib (Mascarenhas and Hoffman, 2012), have been employed in clinical settings but only serve as second-line agents for high-risk patients. Therefore, no ideal treatment options exist for either high-risk or low-risk patients.

Limited treatment options exist for low-risk PV patients despite their elevated risk of thrombosis (~22%), leukemic, or myelofibrotic transformation [~18%; (Cerquozzi et al., 2017)]. Phlebotomy is a conservative treatment that simply removes excessive blood cells, and many adverse effects such as the vessel–vagal reflex and vessel failure can develop after long-term phlebotomy. Therefore, the development of medications to slow disease progression and manage hematocrit in low-risk PV patients remains necessary. This study explored whether alternative medications with antineoplastic or cytoreductive potential exist to slow disease progression.

Drug repositioning is an approach that rapidly repurposes developed compounds or marketed drugs to a new indication on the basis of findings from existing data. The approach can be used to rapidly establish a foundation for the safety, dose range, and pharmacokinetic/pharmacodynamic properties of the drug for the indication of interest (Breckenridge and Jacob, 2019; Pushpakom et al., 2019). As an example of drug repositioning, combinations of DNA methyltransferase inhibitors and histone deacetylase inhibitors have been considered as a strategy for epigenetic therapy in cancer (Pathania et al., 2016). Though the use of therapeutic phlebotomy is commonly employed in PV patients, PV patients were just small portion of participants enrolled in our study. The present study selected hydralazine and valproate as candidates for a drug-repositioning strategy to treat patients who require phlebotomy in this cohort reflecting the whole Taiwan population. Hydralazine was originally used for hypertension management, acting as a known DNA methyltransferase inhibitor (Deng et al., 2003). Valproate is an antipsychotic agent widely used for epilepsy and affective psychosis and was reported to be a histone deacetylase inhibitor (Phiel et al., 2001). The combination of hydralazine and valproate has been studied for various hematological malignancies such as mycosis fungoides (Duenas-Gonzalez et al., 2010), myelodysplastic syndrome (Candelaria et al., 2011; Candelaria et al., 2017), cutaneous T-cell lymphoma (Espinoza-Zamora et al., 2017; Schcolnik-Cabrera et al., 2018), and myeloid leukemia (Cervera et al., 2012; Lubbert et al., 2020). Previous study also demonstrated that hydralazine may have potential of reducing risk of developing to several subgroups of hematologic neoplasms (Yang et al., 2022).

Currently, no pharmacoepidemiological study utilizing hydralazine and valproate as candidates of drug repurposing

for patients who require phlebotomy has been reported. We attempted to validate the potential of hydralazine and valproate in a nationwide cohort by using data from the Taiwan National Health Insurance Research Database from 2000 to 2015 (NHIRD 2000–2015). We calculated the differences in the hazard ratios (HRs) and frequencies of therapeutic phlebotomy for patients with and without hydralazine, valproate, and combination hydralazine–valproate prescriptions.

MATERIALS AND METHODS

Ethics Approval and Consent to Participate

The personal identification data from NHIRD 2000-2015 were encrypted to protect privacy. The protocol of this study was reviewed and approved by the Institutional Review Board of the Tri-Service General Hospital (No.: B-109-38).

Data Source

Data were retrospectively collected from the NHIRD 2000–2015. The Taiwan National Health Insurance program was launched in 1995 and most of the Taiwan population are enrolled (Lin et al., 2018). The NHIRD is a representative cohort that contains detailed registry and claims data, including data from outpatient departments and inpatient hospital care settings from the National Health Insurance Program. The NHIRD collects basic demographic information (such as sex, birthday, and area of residence), insurance premium, prescriptions, operations, examinations, medical visits, and disease diagnoses according to the *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) codes which were all made by board-certified clinicians. The National Health Insurance Administration regularly, retrospectively and randomly reviews the medical records in the NHIRD to verify the accuracy of the diagnoses and that appropriate management was provided. All personally identifying information in the NHIRD was obscured to protect patient privacy. Previous study reported a high quality (94% accuracy) of principal diagnosis (Cheng et al., 2011) in comparison with medical records in one medical center, indicating the accurate database in NHIRD.

Sampled Patients and Outcome Measures

Patients who received the candidate drugs (hydralazine or valproate) were included. Patients who were younger than 20 years, received hydralazine or valproate continuously for less than 180 days, lacked a listed date at which they started receiving the candidate drugs, met the *ICD-9-CM* diagnostic criteria for malignant neoplasms of lymphatic and hematopoietic tissue, or received therapeutic phlebotomy before tracking were excluded. A control group of patients without prescriptions of hydralazine or valproate were matched to patients in the experimental group in a 4:1 ratio in study groups according to age, sex, and index year.

To study the dose-dependent effect of candidate drugs on the occurrence of therapeutic phlebotomy, a stratified analysis was conducted for five dose levels, namely 0%–19%, 20%–39%, 40%–59%, 60%–79%, and 80–100% of the defined daily dose (DDD), which is 300 mg per day for hydralazine and 2000 mg per day for valproate according to maximum daily consumption. The included patients were followed up until the end of the study period (end of 2015). The duration of follow-up represents the interval between the date of inclusion and the date the patient underwent their first therapeutic phlebotomy (*ICD-9-CM*: 94004C). Subsequently, the frequency that the patients received therapeutic phlebotomy was monitored until the end of the study period.

Covariates

The covariates were sex, age groups (20–29, 30–39, 40–49, 50–59, and over 60 years), area of residence (north, central, south, and east Taiwan), level of hospital (medical center, regional hospital, local hospital), and urbanization level of the town of residence (levels 1–4). The urbanization level of the area of residence was defined according to population and several indicators of development. Level 1 was defined as a region with a population of more than 1,250,000 and with a specific designation as a political, economic, cultural, and metropolitan center; level 2 was defined as a region with a population of 500,000 to 1,249,999 and that plays a key role in politics, economy, and culture; levels 3 and 4 were defined as regions with populations of 150,000 to 499,999 and under 149,999, respectively.

The comorbidities were hypertension (*ICD-9-CM*: 401–405), gestational hypertension (*ICD-9-CM*: 642.0–642.3, 642.7, 642.9), idiopathic pulmonary artery hypertension (*ICD-9-CM:* 416.0), congestive heart failure (*ICD-9-CM*: 428), affective psychosis (*ICD-9-CM*: 296), epilepsy (*ICD-9-CM*: 345), migraine (*ICD-9-CM*: 346), pulmonary embolism (PE, *ICD-9-CM*: 415.1), gastric ulcer (*ICD-9-CM*: 531), peptic ulcer disease (*ICD-9-CM*: 533), gastrojejunal ulcer (*ICD-9-CM*: 534), gastrointestinal hemorrhage (GI hemorrhage, *ICD-9-CM*: 578), Budd–Chiari syndrome (*ICD-9-CM*: 453.0), cerebral thrombosis (*ICD-9-CM*: 434.0), ischemic heart disease (*ICD-9-CM*: 411), vascular insufficiency of intestine (*ICD-9-CM*: 557), and Charlson comorbidity index with the aforementioned diseases removed (CCI_R; **Supplementary Table S1**).

Statistical Analysis

The results are presented as HRs with a 95% confidence interval, adjusted for the aforementioned covariates by using multivariate Cox regression analysis. The differences between the four groups (control, hydralazine, valproate, and hydralazine–valproate in combination) were calculated using the Kaplan-Meier method with the log-rank test or the Scheffe post hoc test. The chi-square test was used to compare categorical variables by treatment types when the categorical outcomes were larger than five, and Fisher's exact test was used when the categorical outcomes were smaller than five. A two-tailed p value of < 0.05 was considered significant. All statistical analyses were performed using SPSS (version 22.0, IBM Corp., Armonk, NY, United States).

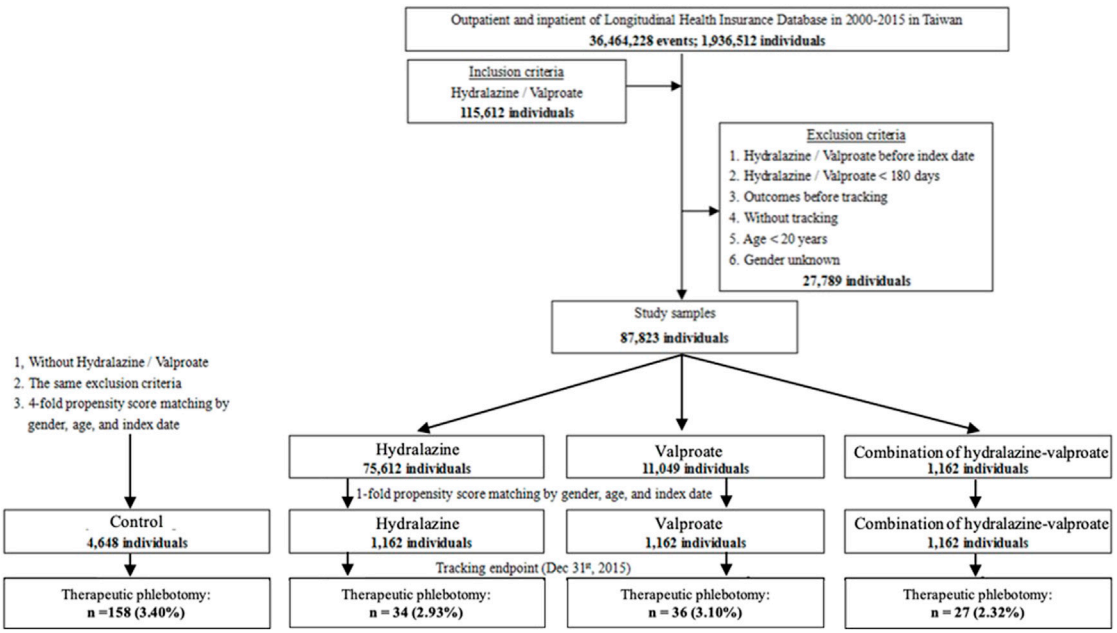


FIGURE 1 | Flowchart of patient enrollment.

RESULTS

Patients Enrolled

A total of 115,612 patients were initially included, of which 27,789 were excluded according to the aforementioned exclusion criteria. Of the remaining 87,823 patients, 75,612 had received a hydralazine prescription, 11,049 had received a valproate prescription, and the remainder (1,162 patients) had received a prescription for both hydralazine and valproate. Two subgroups of 1,162 patients each were randomly created from the hydralazine group and the valproate group. A total of 4,648 enrollees who did not take hydralazine or valproate were selected as controls (**Figure 1**).

The sex ratio (male/female) of patients was 1.15. More than half of the patients were aged >60 years. The percentage of patients with a history of hypertension in the hydralazine group was significantly higher than that in the control and the valproate groups because hypertension is an indication for hydralazine ($p < 0.001$). Similarly, the percentage of patients in the valproate group with a history of affective psychosis, epilepsy, or migraine was significantly higher than that in the control and hydralazine groups ($p < 0.001$). The prevalence of gastric and gastrojejunal ulcer was lower in the valproate and combination groups ($p < 0.001$ for gastric ulcer; $p = 0.010$ for gastrojejunal ulcer). The prevalence of cerebral thrombosis was significantly higher in the combination group ($p < 0.001$). Patients in the hydralazine and combination groups had a higher CCI_R score than those in other groups ($p < 0.001$). In addition, more than 70% of the patients were residents in cities with a high urbanization level (level 1–2). The patients were most likely to be treated in a local hospital, especially those in the hydralazine group (**Supplementary Table S2**).

Factors Correlated With Therapeutic Phlebotomy

In our cohort, patients were more likely to receive therapeutic phlebotomy at higher-level hospitals, in cities with higher levels of urbanization, and between winter and spring. Male patients had a lower risk of meeting the criteria for receiving therapeutic phlebotomy (adjusted HR = 0.766; $p = 0.038$). Patients with hypertension, affective psychosis, gastrojejunal ulcer, GI hemorrhage, ischemic heart disease, and other diseases or conditions included in the Charlson comorbidity index were high-risk populations for receiving therapeutic phlebotomy ($p < 0.05$). By contrast, patients with epilepsy had a lower risk of receiving therapeutic phlebotomy ($p = 0.042$; **Table 1**).

Reduced Cumulative Risk and Decreased Frequency of Therapeutic Phlebotomy

Patients with a combination hydralazine–valproate prescription had a lower cumulative occurrence of therapeutic phlebotomy than did the control, but occurrence in the hydralazine and valproate groups was not significantly lower than that in the control ($p = 0.024$ for the combination group vs. the control, 0.058 for the hydralazine group vs. the control, 0.185 for the valproate group vs. the control). No significant difference in occurrence was observed among the hydralazine, valproate, or combination groups ($p = 0.258$–0.971; **Figure 2**).

The frequency of therapeutic phlebotomy in the hydralazine, valproate, and combination groups was significantly lower than that in the control group ($p = 0.015$), whereas no significant differences were observed among the hydralazine, valproate, and combination groups (**Table 2**).

TABLE 1 | Factors affecting risk of requiring therapeutic phlebotomy determined using Cox regression.

Variables	Adjusted HR	95% CI		*p*
Group				
Control	Reference			
Hydralazine	0.729	0.572	0.991	0.047
Valproate	0.887	0.548	1.131	0.196
Combination of hydralazine-valproate	0.621	0.413	0.934	0.022
Gender				
Male	0.766	0.595	0.985	0.038
Female	Reference			
Age group (yrs)				
20-29	Reference			
30-39	1.562	0.173	4.161	0.992
40-49	2.451	0.134	5.453	0.902
50-59	1.284	0.045	4.27	0.917
≧60	0.986	0.127	5.567	0.903
Season				
Spring	Reference			
Summer	0.633	0.442	0.907	0.013
Autumn	0.496	0.344	0.715	<0.001
Winter	0.907	0.657	1.253	0.554
Urbanization level				
1 (The highest)	1.54	1.009	2.349	0.045
2	1.427	0.968	2.102	0.072
3	1.147	0.627	2.096	0.657
4 (The lowest)	Reference			
Levels of hospitals				
Hospital center	1.246	0.856	1.814	0.250
Regional hospital	1.126	0.806	1.574	0.486
Local hospital	Reference			
Hypertension	1.452	1.326	1.626	<0.001
Gestational Hypertension	0	—	—	0.999
IPAH	1.128	0.114	6.035	0.852
Congestive heart failure	0.961	0.61	1.512	0.862
Affective psychosis	1.199	1.012	1.65	0.017
Epilepsy	0.807	0.326	1.994	0.042
Migraine	0	—	—	0.870
PE	0.863	0.117	6.367	0.885
Gastric ulcer	1.557	0.865	2.804	0.140
Peptic ulcer disease	0.989	0.312	3.132	0.985
Gastrojejunal ulcer	2.11	1.386	5.511	<0.001
GI hemorrhage	2.039	1.24	3.354	0.005
Budd–Chiari syndrome	0.826	0.115	5.935	0.850
Cerebral thrombosis	1.303	0.124	2.171	0.249
Ischemic heart disease	2.532	1.117	5.744	0.026
Vascular insufficiency of intestine	1.69	0.413	6.909	0.465
CCI_R	1.786	1.615	1.976	<0.001

HR, hazard ratio; CI, confidence interval; Adjusted HR, adjusted variables listed in the table, Location had multicollinearity with urbanization level, IPAH, idiopathic pulmonary artery hypertension.

Decreasing HR of Therapeutic Phlebotomy Stratified by Prescription Dose

In the hydralazine group, the HR of undergoing therapeutic phlebotomy was significantly lower even under a low dose (<20% DDD, $p = 0.040$). The HR in the overall hydralazine group was close to the boundary of statistical significance ($p = 0.047$). In the valproate group, only the subgroup with a high dose (>60% DDD) had a significantly lower HR (60–79% DDD; $p = 0.047$; ≥80%; $p = 0.012$). A similar pattern was observed in the combination group; the HR was significantly lower in subgroups with a dose higher than 60% ($p < 0.001$). The dose-dependent effect was strong in the valproate and combination groups but was absent in the hydralazine group (**Table 3**).

Limitations

This retrospective cohort study was based on the NHIRD and employed *ICD-9-CM* codes; thus, some of the data may be

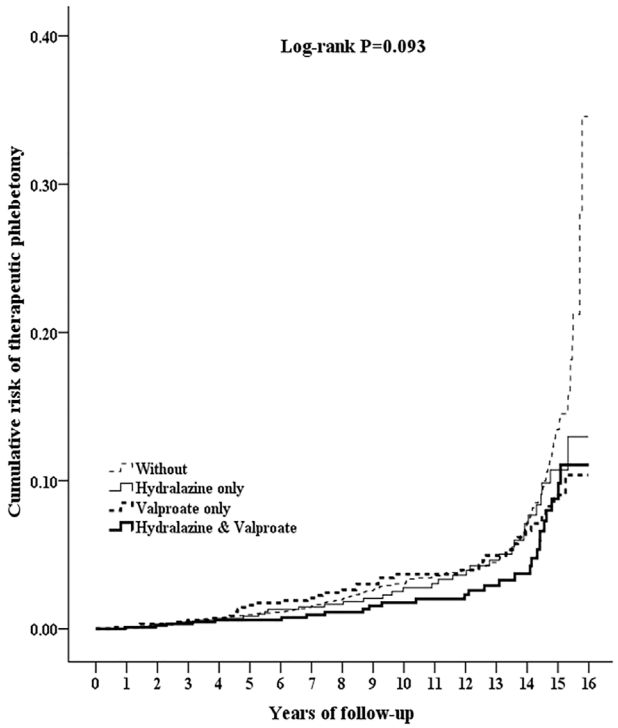


FIGURE 2 | Kaplan–Meier curves for cumulative risk of requiring therapeutic phlebotomy in patients aged ≥20 from different cohorts drawn using the log-rank test. Log-rank test: Control vs. hydralazine, $p = 0.058$; control vs. valproate, $p = 0.185$; control vs. combination hydralazine–valproate, $p = 0.018$; hydralazine vs. valproate, $p = 0.971$; hydralazine vs. combination hydralazine–valproate, $p = 0.258$; valproate vs. combination hydralazine–valproate, $p = 0.318$.

inaccurate. For example, the dose level of treatment was estimated by dividing the cumulative doses of individual medications by the prescription duration. Several indexes such as the volume of phlebotomy, hematocrit content, and the genotype of the oncogene, such as JAK2V617F, were not recorded. Furthermore, body mass index, real income, and lifestyle factors, including smoking/drinking frequency and dietary factors, were not recorded in the NHIRD. The patients whose data are contained in the NHIRD were assumed to be ethnic Taiwanese, with considerable similarity to Southern Han Chinese; a very small portion of the patients may not be ethnic Taiwanese, such as immigrants or foreign residents.

DISCUSSION

For unknown reasons, male patients exhibited a lower occurrence of therapeutic phlebotomy, and therapeutic phlebotomy procedures were most commonly performed in the winter and spring. Whether sex or seasonal factors are correlated with therapeutic phlebotomy merits further study. Some diseases were significantly correlated with a higher rate of therapeutic phlebotomy, especially gastrojejunal ulcer ($p < 0.001$), GI hemorrhage ($p = 0.005$), and hypertension ($p < 0.001$). The contracted plasma volume caused by excess blood cells in PV patients may lead to hypertension (Zeis et al., 1979), and PV may increase the risk of thrombosis, which is typically managed with aspirin. The long-term use of aspirin may induce gastrojejunal ulcer and GI hemorrhage (Cryer and Mahaffey, 2014). Furthermore, gastrojejunal ulcer and GI hemorrhage are common symptoms in patients with PV because of the abnormally high release of histamine by mast cells or increased susceptibility to *H. pylori* infection (Gilbert et al., 1966; Torgano et al., 2002). In addition, psychosis is associated with therapeutic phlebotomy (adjusted HR = 1.199; $p = 0.017$). A model has been proposed to explain psychiatric events resulting from blood hyperviscosity, including slowed blood flow with hypoxia and small, multiple thromboses in the central nervous system (Coelho et al., 2022). Ischemic heart disease was also observed to be associated with frequent therapeutic phlebotomy (adjusted HR = 2.532; $p = 0.026$), which may be caused by the correlation between cyanotic congenital heart disease and secondary polycythemia (Assi and Baz, 2014). Therefore, the aforementioned diseases should be considered comorbidities but not contributing factors.

Patients with epilepsy, which is the original indication of valproate, had a low risk of requiring therapeutic phlebotomy (adjusted HR = 0.807; $p = 0.042$), but the mechanism remains unknown; whether the reduced need for therapeutic phlebotomy in the valproate group was caused by epilepsy or valproate requires further study (**Table 1**).

No dose-dependent effects were observed in the hydralazine group. By contrast, a dose-dependent pattern was observed in the valproate group, but the HRs were significantly lower only for doses up to 60% of DDD (1,200 mg per day). A similar pattern was observed in the combination group (**Table 3**). This may indicate that the mechanisms of action of hydralazine and valproate are independent of each other. Furthermore,

TABLE 2 | Frequency of therapeutic phlebotomy in different groups.

Group	1. Control		2. Hydralazine		3. Valproate		4. Combination of Hydralazine-Valproate		*P*	
Outcomes	***n***	**Mean ± SD, per PY**	***n***	**Mean ± SD, per PY**	***n***	**Mean ± SD, per PY**	***n***	**Mean ± SD, per PY**		**Scheffe post hoc**
Phlebotomy	158	2.27 ± 3.45	34	1.99 ± 2.47	36	2.01 ± 3.26	27	1.86 ± 2.98	0.015	1 > 3 = 2 = 4

P: *One-way ANOVA with Scheffe post hoc.*

TABLE 3 | HR of therapeutic phlebotomy stratified by prescription dose.

Group, Dose (DDD)	Population	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI		*P*
Control	4,648	158	48,055.71	328.79	Reference			
Hydralazine	1,162	34	12,653.22	268.71	0.729	0.572	0.991	0.047
<20%	321	8	3,495.43	228.87	0.621	0.487	0.844	0.040
20-39%	204	7	2,221.39	315.12	0.855	0.671	1.163	0.055
40-59%	334	9	3,636.98	247.46	0.674	0.523	0.912	0.033
60-79%	155	6	1,687.82	355.49	0.964	0.754	1.313	0.062
≧80%	148	4	1,611.60	248.20	0.673	0.521	0.915	0.036
Valproate	1,162	36	12,707.30	283.30	0.887	0.548	1.131	0.196
<20%	287	8	3,138.55	254.89	0.798	0.490	1.026	0.178
20-39%	219	9	2,394.92	375.80	1.076	0.723	1.512	0.226
40-59%	301	10	3,291.65	303.80	0.942	0.587	1.218	0.203
60-79%	189	5	2,066.85	241.91	0.757	0.465	0.996	0.047
≧80%	166	4	1,815.33	220.35	0.691	0.423	0.880	0.012
Combination of hydralazine-valproate	1,162	27	12,754.98	211.68	0.621	0.413	0.934	0.022
<20%	105	4	1,284.90	311.31	0.842	0.682	1.112	0.142
20-39%	119	4	1,229.75	325.27	0.942	0.735	1.267	0.206
40-59%	197	6	2,038.15	294.38	0.758	0.595	1.086	0.078
60-79%	158	3	1,683.45	178.21	0.582	0.297	0.864	<0.001
≧80%	583	10	6,518.73	153.40	0.429	0.198	0.726	<0.001

PYs, Person-years.
Adjusted HR, adjusted hazard ratio, adjusted by the variates listed in ***Table 1****.*
CI, confidence interval.
DDD for hydralazine = 300 mg per day, for valproate = 2000 mg per day.

hydralazine was reported to induce lupus syndromes (incidence >5% when doses were up to 100 mg per day) in a cohort study (n = 281), whereas no lupus event was observed in a group with doses of 50 mg per day (Cameron and Ramsay, 1984). A lower dose of hydralazine (<20% of DDD, <60 mg per day) might be less likely to cause lupus syndromes and be efficacious in reducing the need for therapeutic phlebotomy (adjusted HR = 0.621; p = 0.040; **Table 3**). We suggest that further dose-finding studies use initial doses of less than 60 mg per day.

In addition to the reduction in phlebotomy frequency, inhibitory efficacy of cell survival rate was also disclosed on leukocytes of chronic myeloproliferative patients after treatment of hydralazine and valproate in previous work (Yang et al., 2022). There are two phlebotomy volume, 250 ml or 500 ml once a time of phlebotomization, applied for patients by Taiwan physician's order. The therapeutic code of 94004C represents performing once phlebotomization in NHIRD. In spite of the difference between 250 and 500 ml per phlebotomization, our study disclosed that the frequency of undergoing phlebotomy significantly decreased from 2.27 to 1.99 per year in patients with regular prescription of hydralazine. Although the overall results indicate that combination hydralazine–valproate may act as an efficient cytoreductive agent and may ensure greater cytoreductive potential for patients who require therapeutic phlebotomy than hydralazine alone, the combination of the two may not be ideal as an additional treatment for patients who require phlebotomy. In this study, a low proportion of the patients met the criteria to take both hydralazine and valproate (**Figure 1**), and the standard medication for patients with PV, aspirin, is known to increase plasma concentrations of valproate and hamper its metabolism (Sandson et al., 2006).

Considering the risk–benefit balance of drug repurposing for clinical decision-making, we suggest that hydralazine, instead of combination valproate–hydralazine, could be feasible for patients who require regular phlebotomy.

DATA AVAILABILITY STATEMENT

The datasets used in this study are available from the Taiwan NHIRD. Because of legal restrictions imposed by the government of Taiwan in relation to the Personal Information Protection Act, data cannot be made publicly available. Requests for data can be sent as a formal proposal to the NHIRD (http://nhird.nhri.org.tw).

ETHICS STATEMENT

The study involving human participants was reviewed and approved by the Institutional Review Board of Tri-Service General Hospital (No.:B-109-38).

AUTHOR CONTRIBUTIONS

W-ZL: Study conceptualization, data interpretation, and manuscript writing. C-HC: Data acquisition. C-YS: Data interpretation. B-HY: Study conceptualization, English editing, data interpretation, and overall direction. W-CC: Study conceptualization, project administration, and funding acquisition. All authors have read and approved the final manuscript.

FUNDING

This study was supported by the Tri-Service General Hospital Research Foundation (TSGH-B-111-018) and Ministry of National Defense-Medical Affairs Bureau (MAB 106-036, MAB 107-023). The funders have no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All authors declare no other competing interests.

ACKNOWLEDGMENTS

We thank Dr. Yeu-Chin Chen (Division of Hematology and Oncology, Department of Medicine, Tri-Service General Hospital) for support with the study design and analysis, and Ms. Miranda Loney, US Board of Editors in the Life Sciences certified editor, for English editing. This manuscript was edited by Wallace Academic Editing. We also appreciate the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW), Taiwan, for providing the National Health Insurance Research Database (NHIRD).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.850045/full#supplementary-material

REFERENCES

Alvarez-Larrán, A., Pérez-Encinas, M., Ferrer-Marín, F., Hernández-Boluda, J. C., Ramírez, M. J., Martínez-López, J., et al. (2017). Risk of Thrombosis According to Need of Phlebotomies in Patients with Polycythemia Vera Treated with Hydroxyurea. *Haematologica* 102, 103–109. doi:10.3324/haematol.2016.152769

Alvarez-Larrán, A., Pereira, A., Cervantes, F., Arellano-Rodrigo, E., Hernández-Boluda, J. C., Ferrer-Marín, F., et al. (2012). Assessment and Prognostic Value of the European LeukemiaNet Criteria for Clinicohematologic Response, Resistance, and Intolerance to Hydroxyurea in Polycythemia Vera. *Blood* 119, 1363–1369. doi:10.1182/blood-2011-10-387787

Arber, D. A., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M. J., Le Beau, M. M., et al. (2016). The 2016 Revision to the World Health Organization Classification of Myeloid Neoplasms and Acute Leukemia. *Blood* 127, 2391–2405. doi:10.1182/blood-2016-03-643544

Assi, T. B., and Baz, E. (2014). Current Applications of Therapeutic Phlebotomy. *Blood Transfus.* 12 Suppl 1 (Suppl. 1), s75–83. doi:10.2450/2013.0299-12

Barbui, T., Carobbio, A., Ghirardi, A., Masciulli, A., Rambaldi, A., and Vannucchi, A. M. (2017). No Correlation of Intensity of Phlebotomy Regimen with Risk of Thrombosis in Polycythemia Vera: Evidence from European Collaboration on Low-Dose Aspirin in Polycythemia Vera and Cytoreductive Therapy in Polycythemia Vera Clinical Trials. *Haematologica* 102, e219–e221. doi:10.3324/haematol.2017.165126

Breckenridge, A., and Jacob, R. (2019). Overcoming the Legal and Regulatory Barriers to Drug Repurposing. *Nat. Rev. Drug Discov.* 18, 1–2. doi:10.1038/nrd.2018.92

Cameron, H. A., and Ramsay, L. E. (1984). The Lupus Syndrome Induced by Hydralazine: a Common Complication with Low Dose Treatment. *Br. Med. J. (Clin Res. Ed.)* 289, 410–412. doi:10.1136/bmj.289.6442.410

Campbell, P. J., Scott, L. M., Buck, G., Wheatley, K., East, C. L., Marsden, J. T., et al. (2005). United Kingdom Myeloproliferative Disorders Study, G., Medical Research Council Adult Leukaemia WorkingDefinition of Subtypes of Essential Thrombocythaemia and Relation to Polycythaemia Vera Based on JAK2 V617F Mutation Status: a Prospective Study. *Lancet* 366, 1945–1953. doi:10.1016/s0140-6736(05)67785-9

Candelaria, M., Herrera, A., Labardini, J., González-Fierro, A., Trejo-Becerril, C., Taja-Chayeb, L., et al. (2011). Hydralazine and Magnesium Valproate as Epigenetic Treatment for Myelodysplastic Syndrome. Preliminary Results of a Phase-II Trial. *Ann. Hematol.* 90, 379–387. doi:10.1007/s00277-010-1090-2

Candelaria, M., Burgos, S., Ponce, M., Espinoza, R., and Dueñas-Gonzalez, A. (2017). Encouraging Results with the Compassionate Use of Hydralazine/valproate (TRANSKRIP™) as Epigenetic Treatment for Myelodysplastic Syndrome (MDS). *Ann. Hematol.* 96, 1825–1832. doi:10.1007/s00277-017-3103-x

Cerquozzi, S., Barraco, D., Lasho, T., Finke, C., Hanson, C. A., Ketterling, R. P., et al. (2017). Risk Factors for Arterial versus Venous Thrombosis in Polycythemia Vera: a Single center Experience in 587 Patients. *Blood Cancer J.* 7, 662. doi:10.1038/s41408-017-0035-6

Cervera, E., Candelaria, M., López-Navarro, O., Labardini, J., Gonzalez-Fierro, A., Taja-Chayeb, L., et al. (2012). Epigenetic Therapy with Hydralazine and Magnesium Valproate Reverses Imatinib Resistance in Patients with Chronic Myeloid Leukemia. *Clin. Lymphoma Myeloma Leuk.* 12, 207–212. doi:10.1016/j.clml.2012.01.005

Cheng, C. L., Kao, Y. H., Lin, S. J., Lee, C. H., and Lai, M. L. (2011). Validation of the National Health Insurance Research Database with Ischemic Stroke Cases in Taiwan. *Pharmacoepidemiol. Drug Saf.* 20, 236–242. doi:10.1002/pds.2087

Coelho, R. O., Reynaldo, L. F. M., Valente, G., and Silva, L. F. (2022). Outcome of Patient with Polycythemia Rubra Vera and Psychiatric Symptoms. *Hematol. Transfus. Cel Ther.* 44, 116–119. doi:10.1016/j.htct.2020.06.010

Cryer, B., and Mahaffey, K. W. (2014). Gastrointestinal Ulcers, Role of Aspirin, and Clinical Outcomes: Pathobiology, Diagnosis, and Treatment. *J. Multidiscip Healthc.* 7, 137–146. doi:10.2147/JMDH.S54324

Deng, C., Lu, Q., Zhang, Z., Rao, T., Attwood, J., Yung, R., et al. (2003). Hydralazine May Induce Autoimmunity by Inhibiting Extracellular Signal-Regulated Kinase Pathway Signaling. *Arthritis Rheum.* 48, 746–756. doi:10.1002/art.10833

Dueñas-Gonzalez, A., Vega, M. T., Martinez-Baños, D., García-Hidalgo, L., and Sobrevilla, P. (2010). Response to Hydralazine-Valproate in a Patient with Mycosis Fungoides. *Case Rep. Med.* 2010, 657579. doi:10.1155/2010/657579

Espinoza-Zamora, J. R., Labardini-Méndez, J., Sosa-Espinoza, A., López-González, C., Vieyra-García, M., Candelaria, M., et al. (2017). Efficacy of Hydralazine and Valproate in Cutaneous T-Cell Lymphoma, a Phase II Study. *Expert Opin. Investig. Drugs* 26, 481–487. doi:10.1080/13543784.2017.1291630

Gilbert, H. S., Warner, R. R., and Wasserman, L. R. (1966). A Study of Histamine in Myeloproliferative Disease. *Blood* 28, 795–806. doi:10.1182/blood.v28.6.795.795

Kim, S. Y., Bae, S. H., Bang, S. M., Eom, K. S., Hong, J., Jang, S., et al. (2021). The 2020 Revision of the Guidelines for the Management of Myeloproliferative Neoplasms. *Korean J. Intern. Med.* 36, 45–62. doi:10.3904/kjim.2020.319

Landtblom, A. R., Bower, H., Andersson, T. M., Dickman, P. W., Samuelsson, J., Björkholm, M., et al. (2018). Second Malignancies in Patients with Myeloproliferative Neoplasms: a Population-Based Cohort Study of 9379 Patients. *Leukemia* 32, 2203–2210. doi:10.1038/s41375-018-0027-y

Levine, R. L., Wadleigh, M., Cools, J., Ebert, B. L., Wernig, G., Huntly, B. J., et al. (2005). Activating Mutation in the Tyrosine Kinase JAK2 in Polycythemia Vera, Essential Thrombocythemia, and Myeloid Metaplasia with Myelofibrosis. *Cancer Cell* 7, 387–397. doi:10.1016/j.ccr.2005.03.023

Lin, L. Y., Warren-Gash, C., Smeeth, L., and Chen, P. C. (2018). Data Resource Profile: the National Health Insurance Research Database (NHIRD). *Epidemiol. Health* 40, e2018062. doi:10.4178/epih.e2018062

Lübbert, M., Grishina, O., Schmoor, C., Schlenk, R. F., Jost, E., Crysandt, M., et al. (2020). Valproate and Retinoic Acid in Combination with Decitabine in Elderly Nonfit Patients with Acute Myeloid Leukemia: Results of a Multicenter, Randomized, 2 × 2, Phase II Trial. *J. Clin. Oncol.* 38, 257–270. doi:10.1200/JCO.19.01053

Ma, X., Vanasse, G., Cartmel, B., Wang, Y., and Selinger, H. A. (2008). Prevalence of Polycythemia Vera and Essential Thrombocythemia. *Am. J. Hematol.* 83, 359–362. doi:10.1002/ajh.21129

Mascarenhas, J., and Hoffman, R. (2012). Ruxolitinib: the First FDA Approved Therapy for the Treatment of Myelofibrosis. *Clin. Cancer Res.* 18, 3008–3014. doi:10.1158/1078-0432.CCR-11-3145

Pathania, R., Ramachandran, S., Mariappan, G., Thakur, P., Shi, H., Choi, J. H., et al. (2016). Combined Inhibition of DNMT and HDAC Blocks the Tumorigenicity of Cancer Stem-like Cells and Attenuates Mammary Tumor Growth. *Cancer Res.* 76, 3224–3235. doi:10.1158/0008-5472.CAN-15-2249

Phiel, C. J., Zhang, F., Huang, E. Y., Guenther, M. G., Lazar, M. A., and Klein, P. S. (2001). Histone Deacetylase Is a Direct Target of Valproic Acid, a Potent Anticonvulsant, Mood Stabilizer, and Teratogen. *J. Biol. Chem.* 276, 36734–36741. doi:10.1074/jbc.M101287200

Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., et al. (2019). Drug Repurposing: Progress, Challenges and Recommendations. *Nat. Rev. Drug Discov.* 18, 41–58. doi:10.1038/nrd.2018.168

Sandson, N. B., Marcucci, C., Bourke, D. L., and Smith-Lamacchia, R. (2006). An Interaction between Aspirin and Valproate: the Relevance of Plasma Protein Displacement Drug-Drug Interactions. *Am. J. Psychiatry* 163, 1891–1896. doi:10.1176/ajp.2006.163.11.1891

Schcolnik-Cabrera, A., Domínguez-Gómez, G., and Dueñas-González, A. (2018). Comparison of DNA Demethylating and Histone Deacetylase Inhibitors Hydralazine-Valproate versus Vorinostat-Decitabine Incutaneous T-Cell Lymphoma in HUT78 Cells. *Am. J. Blood Res.* 8, 5–16.

Scott, L. M., Tong, W., Levine, R. L., Scott, M. A., Beer, P. A., Stratton, M. R., et al. (2007). JAK2 Exon 12 Mutations in Polycythemia Vera and Idiopathic Erythrocytosis. *N. Engl. J. Med.* 356, 459–468. doi:10.1056/NEJMoa065202

Talpaz, M., and Kiladjian, J. J. (2021). Fedratinib, a Newly Approved Treatment for Patients with Myeloproliferative Neoplasm-Associated Myelofibrosis. *Leukemia* 35, 1–17. doi:10.1038/s41375-020-0954-2

Torgano, G., Mandelli, C., Massaro, P., Abbiati, C., Ponzetto, A., Bertinieri, G., et al. (2002). Gastroduodenal Lesions in Polycythaemia Vera: Frequency and Role of *Helicobacter pylori*. *Br. J. Haematol.* 117, 198–202. doi:10.1046/j.1365-2141.2002.03380.x

Yang, B. H., Lin, W. Z., Chiang, Y. T., Chen, Y. C., Chung, C. H., Chien, W. C., et al. (2022). Epigenetics-Associated Risk Reduction of Hematologic Neoplasms in a Nationwide Cohort Study: The Chemopreventive and Therapeutic Efficacy of Hydralazine. *Front. Oncol.* 12, 809014. doi:10.3389/fonc.2022.809014

Zeis, P. M., Rao, S., John, E. G., and Aschinberg, L. C. (1979). "Stress" Polycythaemia and Peripheral Facial Palsy Complications of Severe Hypertension. *Acta Paediatr. Scand.* 68, 287–289. doi:10.1111/j.1651-2227.1979.tb05006.x

Conflict of Interest: Author C-YS was employed by company Fidelity Regulation Therapeutics Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 05 April 2022
doi: 10.3389/fphar.2022.815719

Impact of Three Safety Interventions Targeting Off-Label Use of Immediate-Release Fentanyl on Prescription Trends: Interrupted Time Series Analysis

Aníbal García-Sempere[1,2], *Isabel Hurtado*[1,2]*, *Salvador Peiró*[1,2], *Francisco Sánchez-Sáez*[1,2], *Clara Liliana Rodríguez-Bernal*[1,2], *Magda Puig-Ferrer*[3], *Manuel Escolano*[3] and *Gabriel Sanfélix-Gimeno*[1,2]

[1]Foundation for the Promotion of Health and Biomedical Research of Valencia Region, FISABIO, Valencia, Spain, [2]Spanish Network for Chronic Health Services Research, REDISSEC, Valencia, Spain, [3]General Directorate for Pharmacy, Valencia Health System, Valencia, Spain

OPEN ACCESS

Edited by:
Mina Tadrous,
Women's College Hospital, Canada

Reviewed by:
Jason Bondoc Alipio,
University of Maryland, Baltimore, United States
Scott Vouri,
University of Florida, United States

***Correspondence:**
Isabel Hurtado
Hurtado_isa@gva.es

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: 15 November 2021
Accepted: 14 March 2022
Published: 05 April 2022

Citation:
García-Sempere A, Hurtado I, Peiró S, Sánchez-Sáez F, Rodríguez-Bernal CL, Puig-Ferrer M, Escolano M and Sanfélix-Gimeno G (2022) Impact of Three Safety Interventions Targeting Off-Label Use of Immediate-Release Fentanyl on Prescription Trends: Interrupted Time Series Analysis. Front. Pharmacol. 13:815719. doi: 10.3389/fphar.2022.815719

Background: The Spanish health authorities are concerned by the off-label use of immediate-release formulations of fentanyl (IRF) in noncancer pain and cancer pain in patients with no chronic pain therapy.

Aim: To evaluate the impact of different interventions to improve appropriateness of IRF prescription on off-label prescription.

Patients and methods: We used interrupted time series (ITS) to estimate immediate and trend changes of IRF prescription for noncancer pain (NCP) and breakthrough cancer pain (BCP) in patients with and without chronic cancer pain therapy associated with two medication reviews (I1 and I2) and the issue of a safety warning letter (I3) with data from a Spanish region with 5 million inhabitants, from 2015 to 2018.

Results: The use of IRF for NCP in the region Valencia was reduced from about 1,800 prescriptions per week to around 1,400. The first medication review was followed by an immediate level change of −192.66 prescriptions per week ($p < 0.001$) and a downward trend change of −6.75 prescriptions/week ($p < 0.001$), resulting in a post-intervention trend of −1.99 ($p < 0.001$). I2 was associated with a trend change of -23.07 ($p < 0.001$) prescriptions/week. After I3, the trend changed markedly to 27.23 additional prescriptions/week, for a final post-intervention trend of 2.17 ($p < 0.001$). Controlled-ITS provided comparable results. For potentially inappropriate BCP use, the second medication review was followed by a downward, immediate level change of −10.10 prescriptions/week ($p = 0.011$) and a trend change of 2.31 additional prescriptions/week ($p < 0.001$) and the issue of the safety warning (I3) was followed by a downward trend change of −2.09 prescriptions/week ($p = 0.007$).

Conclusion: Despite IRF prescription for NCP decreased, the interventions showed modest and temporary effect on off-label prescription. Our results call for a review of the design and implementation of safety interventions addressing inappropriate opioid use.

Keywords: fentanyl, appropriateness of prescription, interrupted time series, policy interventions, pharmacoepidemiology

INTRODUCTION

Although the patterns of use of opioids in Europe are not comparable to the devastating misuse and overuse phenomenon that occurred in the United States in the 2010s, many European countries report an increasing trend in the use of opioids, and some of them are amongst the largest consumers of strong opioids worldwide (Häuser et al., 2021). Among the latter, fentanyl intake has recently seen unprecedented growth and is the most frequently used strong opioid in several countries, including Spain (Hider-Mlynarz et al., 2018; Bosetti et al., 2019; Hurtado et al., 2020; Salazar et al., 2020).

Over the last years, Spanish health authorities have been concerned by the observed prescribing trends of immediate-release formulations of fentanyl (IRF), a drug 80 to 100 times stronger than morphine, which use is associated with a potential high risk of misuse, abuse, addiction, overdose and serious complications (U.S. Food and Drug Administration, 2014; González-Bermejo et al., 2021a). IRF is approved in Spain for use in patients with breakthrough cancer pain (BCP) who are already on chronic treatment for cancer pain (Spanish Agency of Medicines and Medical Devices, 2021a), but there is compelling evidence of its off-label use in noncancer pain (NCP) and in patients with cancer but not on chronic cancer pain treatment. The rate of first prescriptions of IRF in primary care prescribed for NCP in 2016 was 40% (Spanish Agency of Medicines and Medical Devices, 2021b), and over the past few years 60% of reported cases of IRF-related abuse and dependence have been linked to off-label use (González-Bermejo et al., 2021b).

In this context, different interventions have been implemented to improve the appropriateness of IRF prescription. In the region of Valencia, an eastern territory with five million inhabitants, the growing trend of IRF use led the Valencia Health System (VHS) to implement a medication review intervention on 4 January 2016, mandating the regional pharmacy services to case-by-case audit all IRF prescriptions issued in the region for NCP diagnoses, high dose use of IRF and prescription for BCP in patients with no cancer pain maintenance therapy. Pharmacists contacted prescribers individually with the aim to perform a shared assessment of the appropriateness of their prescriptions for IRF in the aforementioned cases, as well as for establishing different therapeutic targets: interruption of IRF, switch to switch to non-opioid analgesic, tapering strategies, or addition to or substitution with pain maintenance therapy in the case of cancer patients (Valencia Regional Governm, 2021). Later, on 16 October 2017, a second medication review intervention was implemented in the region that included as well a case-by-case audit focusing on prescriptions of IRF for NCP but added administrative hurdles and measures for NCP prescribing, such as the need to fulfil additional formularies and to obtain informed consent from the patient in case of continuation of off-label IRF therapy after the review. According to internal documentation of the General Directorate for Pharmacy of the VHS, these two interventions resulted in discontinuation or modification of about a third of IRF treatments in the region during the period they were enforced, but their long-term impact on the volume of prescription remains unknown. Finally, on 21 February 2018, the Spanish Agency of Medicines issued a Safety Warning Letter on IRF use. Warning Letters are informative documents that are disseminated among all the prescribers in the country and are conceived as a reminder of information and to make recommendations. In this case the Letter reminded of the importance of strictly respecting the approved indications of IRF when prescribing and recommended alternatives to IRF treatment in patients with NCP (Spanish Agency of Medicines and Medical Devices, 2021b).

The aim of this study was to assess the impact of the two regional interventions and the national safety warning on the trends of IRF prescription for NCP and BCP in the region of Valencia for the period 2015–2018.

METHODS

Study Design

In this population-based, quasi-experimental study, we used interrupted time series analyses with data from a 205-week period to evaluate the changes in the number of weekly prescriptions of IRF for NCP and BCP, in patients with or without chronic pain therapy, associated with the implementation of three different interventions targeting non-approved use.

Setting

The study took place in the region of Valencia (Spain) and, specifically, in the population covered by the public Valencia Health System (VHS), which comprises about 97% of the region's inhabitants. We included all prescriptions for IRF issued in the region from 1 January 2015, to 30 November 2018. To determine overlapping chronic cancer pain, we also included all the prescriptions of strong opioids issued in the region during that same period indicated for chronic cancer pain control (extended-release formulations of morphine, oxycodone or tapentadol; transdermal fentanyl or buprenorphine, and hydromorphone) prescribed to patients who had at least one IRF prescription for BCP.

Interventions

We aimed to assess the effect of three interventions on IRF use: a medication review starting on week 53 and lasting for 10 weeks (I1: from 4 January 2016, to 10 March 2016), a second medication review at week 146 and lasting for 6 weeks (I2: from 17 October 2017, to 1 December 2017), and the issue of a Safety Warning letter of the Spanish Agency of Medicines on week 164 (I3).

Data Sources

Data were obtained from the VHS Integrated Database (VID). VID is the result of the linkage, by means of a single personal identification number, of a set of publicly-owned, population-based healthcare, clinical and administrative electronic databases in Valencia, which has provided comprehensive information of the region's five million inhabitants since 2008. VID includes sociodemographic and administrative data as well as healthcare information such as diagnoses, procedures, laboratory data, pharmaceutical prescriptions and dispensing (including brand and generic name, formulation, strength, and dosing schedule/regimen), hospitalizations, mortality, healthcare utilization and public health data (García-Sempere et al., 2020).

Outcomes and Treatment Characterization

We evaluated the impact of three interventions on the trend of weekly prescriptions of IRF. IRF prescriptions were allocated to weeks based on the prescription date. We classified IRF prescriptions into NCP or BCP based on the indication associated with each prescription, using ICD-9 codes and the classification for types of pain proposed by Zhu et al. (2019). For NCP, we further stratified prescriptions into chronic NCP and acute NCP. A marginal proportion of prescriptions (n: 1,140, 0.05% of the total volume) was not associated with a pain diagnose and was excluded from analyses. For prescriptions associated with BCP indications, we determined the presence or absence of chronic treatment for cancer pain by checking at the individual-patient level whether the date of the prescription of IRF was also covered by opioid chronic pain control medication. Days covered with chronic cancer pain medication were estimated using the dosing and regimen scheduled in each prescription.

Statistical Analysis

First, we constructed weekly series of IRF prescriptions for NCP and for BCP in patients with and without chronic cancer pain therapy. Second, we used interrupted time series (ITS) and segmented linear regression models to assess changes in IRF utilization for NCP while controlling for previous levels and trends after the three intervention dates, and we further stratified the analyses for chronic NCP and acute NCP. Third, in order to control for potential confounding and to contrast the results of the previous analysis, we employed controlled-ITS, using the weekly series of prescriptions of IRF for BCP in patients receiving chronic cancer therapy as a control group. This group fulfils the key features for a control group, as it is expected to be unaffected by the intervention (appropriate care) and to share potential confounders with the intervention series (Bottomley et al., 2019).

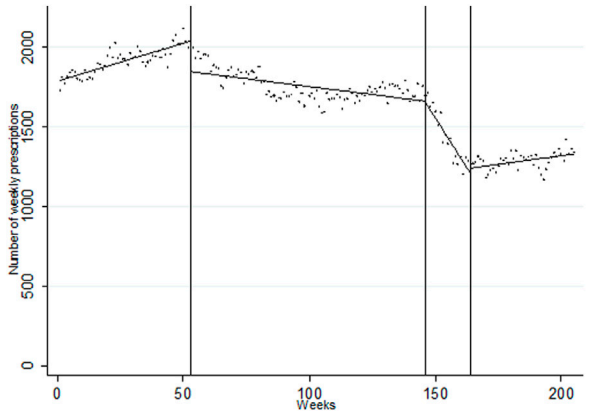


FIGURE 1 | Segmented linear regression trends of weekly series of IRF prescription for NCP, 2015–2018. Dots: observed weekly volume of prescription; Lines: predicted weekly volume of prescription. Week 0: first week of January 2015; Week 53: first medication review; Week 146: second medication review: Week 164: issue of safety warning. Week 205: last week of November 2018. Created by the authors.

Fourth, we evaluated the impact of the interventions on the trends of BCP prescription in patients with and without chronic cancer pain treatment. For all analyses, we first ran ordinary least squares regressions, but the Durbin Watson (DW) test identified serial autocorrelation in the residuals. To account for it, we then used Prais–Winsten regression models and the corresponding DW test (Kobayashi, 1985; Huitema, 2011). We finally estimated the post-intervention trend statistic. All analyses were performed using Stata14 (StataCorp LP, College Station, TX).

RESULTS

Noncancer Pain

A total of 342,595 IRF prescriptions for NCP were issued in the period. From an initial constant of 1,791 weekly prescriptions, an upward trend of 4.75 additional prescriptions per week was observed until I1, when an immediate level change of −192.66 prescriptions per week ($p < 0.001$) and a downward trend change of −6.75 prescriptions/week occurred ($p < 0.001$), resulting in a post-intervention trend of −1.99 ($p < 0.001$). I2 was associated with a trend change of −23.07 ($p < 0.001$) leading to a downward post-intervention trend of −29.06 prescriptions/week ($p < 0.001$). After I3, the trend changed markedly to 27.23 additional prescriptions/week, for a final post-intervention trend of 2.17 ($p < 0.001$; see **Figure 1** and **Table 1**). In controlled-ITS using IRF prescription in BCP in patients with chronic pain therapy series as a control group, relative intervention effects were comparable, with a downward relative trend initiating after I1 (−7.01, $p < 0.001$), accentuated after I2 (−25.14, $p < 0.001$) and a change upwards after I3 (27.64, $p < 0.001$; see **Figure 2** and **Table 1**). When stratifying the analyses by chronic (282,628 prescriptions, or 82.5% of NCP prescription) and acute (59,967 prescriptions) noncancer pain treatment we obtained

TABLE 1 | Segmented regression parameters for IRF use for NCP and NCP with a control group.

NCP	**Coef.**	**Std. Err.**	**t**	**P>|t|**	**[95% conf**	**. Interval]**
Prev. slope	4.76	0.85	5.57	0.000	3.07	6.44
I1 (week 53)						
Level change	−192.66	31.62	−6.09	0	−255.01	−130.30
Slope change	−6.75	1.03	−6.052	0.000	−8.79	−4.71
PI trend	−1.99	0.45	−4.43	0.000	−2.88	−1.10
I2 (week 146)						
Level change	−5.21	31.25	−0,0.7	0.870	−66.83	56.41
Slope change	−23.07	3.74	−6.17	0.000	−30.45	−15.69
PI trend	−25.06	3.63	−6.91	0.000	−32.22	−17.91
I3 (week 164)						
Level change	36.28	44.69	0.81	0.418	−51.85	124.41
Slope change	27.23	4.14	6.58	0.000	19.07	35.40
PI trend	2.17	1.07	2.02	0.044	0.056	4.28
Constant	1791.11	24.39	73.42	0.000	1743.00	1839.22
NCP vs. BCPa	**Coef.**	**Std. Err.**	**t**	**P>|t|**	**[95% Conf**	**. Interval]**
Prev. slope	2.72	1.95	2.2	0.023	0.37	5.07
I1 (week 53)						
Level change	−44.39	41.16	−1	0.281	−125.31	36.53
Slope change	−7.01	1.45	−4.8	0.000	−9.87	−4.16
PI tren diff.	−4.29	0.62	6.94	0.000	−5.51	−3.08
I2 (week 146)						
Level change	39.14	45.79	0.80	0.393	−50.88	129.17
Slope change	−25.14	4.91	−5.10	0.000	−34.80	−15.48
PI trend diff.	−29.43	4.73	−6.23	0.000	−38.72	−20.15
I3 (week 164)						
Level change	70.93	56.39	1.20	0.209	−39.93	181.78
Slope change	27.64	5.48	5.00	0.000	16.86	38.42
PI tren diff.	−1.79	1.67	−1.07	0.286	−5.08	1.50
Constant	968.60	22.82	42.40	0.000	923.74	1013.46
Durbin Watson statistic						
NCP	2.315650					
NCP vs. BCPa	2.316795					

NCP, noncancer pain; BCPa, breakthrough cancer pain in patients with overlapping chronic pain therapy (appropriate); I1,I2, I3, first medication review, second medication review and national safety warning, respectively; PI trend, post-intervention trend; PI trend diff., difference in post-intervention trends between the intervention and control groups.
Created by the authors.

similar results in terms of directionality and intensity (see **Supplementary Material S1**).

Breakthrough Cancer Pain

A total of 246150 IRF prescriptions for cancer pain were issued in the period, of which 19,418 (7.89%) were prescribed in the absence of chronic cancer pain therapy. The trend of prescription of IRF for BCP in patients on chronic treatment for cancer pain rose throughout the period and was unaffected by the interventions, even if I1 was associated with a significant, immediate downward level change (−152.26, $p < 0.001$; see **Figure 3A** and **Table 2**). With regard to the prescription of IRF for BCP in patients with no overlapping chronic therapy, we found that from an initial constant of 95.70 prescriptions per week, the weekly series of IRF prescriptions was relatively stable until I2. I2 was followed by a downward, immediate level change of −10.10 prescriptions/week ($p = 0.011$) and a trend change of 2.31 additional prescriptions/week ($p < 0.001$). The issue of the

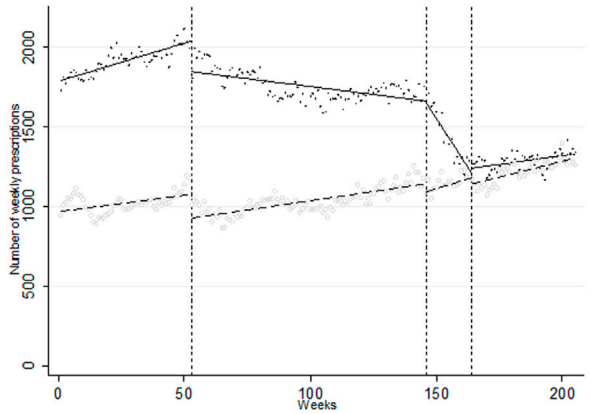


FIGURE 2 | Segmented linear regression trends of weekly series of IRF prescription for NCP using the weekly series of IRF prescription for BCP in patients with chronic cancer pain treatment as a control group, 2015–2018. Crosses/circles: observed weekly volume of prescription for NCP and BCP, respectively; Line/dotted line: predicted weekly volume of prescription for NCP and BCP, respectively. Week 0: first week of January 2015; Week 53: first medication review; Week 146: second medication review: Week 164: issue of safety warning. Week 205: last week of November 2018. Created by the authors.

safety warning (I3) was followed by a downward trend change of −2.09 prescriptions/week ($p = 0.007$; see **Figure 3B** and **Table 2**).

DISCUSSION

The use of IRF for NCP in the region Valencia was reduced from about 1,800 prescription per week to around 1,400 in the period 2015–2018. The two regional medication reviews impacted downwards prescription trends, whereas the issue of the national safety warning was followed by a shift towards an increase of IRF prescription. Regarding use for BCP, the interventions did not seem to affect trends or only very marginally. The use of IRF for BCP in patients with chronic cancer pain therapy increased from about 1000 prescriptions per week to levels similar to those of NCP use at the end of the period.

Even though the volume of IRF prescription for NCP decreased, the interventions showed modest or temporary effect on prescription trends. The first medication review changed successfully long-term trends of IRF use for NCP, but the rate of decline of prescription post-intervention was limited. On the other hand, the second intervention, which incorporated additional hurdles to off-label prescribing, achieved a steadier reduction of prescription that lasted only while the intervention was implemented. Shortly after the end of the intervention, a gradual recovery of the number of prescriptions can be observed. In this sense, the drastic trend change after the issue of the Safety Warning detected by ITS modelling should be interpreted with caution, as it probably speaks more of a combination of the lack of impact of the Safety Warning and a *rebound effect* in prescription happening as a response of the ending of the intensive medication review intervention, than of an effect attributable to the national warning. These findings highlight the need to carefully consider potential trade-offs between the intensity and design of interventions and their impact on short and long-term prescribing behaviour.

The volume of use of IRF for BCP in patients without chronic cancer pain treatment was relatively stable in the period, and the interventions showed no or only small effect on prescription trends. In this sense, our data show that a small but potentially concerning use of IRF in these patients in a non-approved indication is maintained throughout the period (accounting for 7.89% of the total prescription for BCP) and is barely affected by the interventions. On the other hand, prescription for BCP in patients with chronic cancer pain treatment

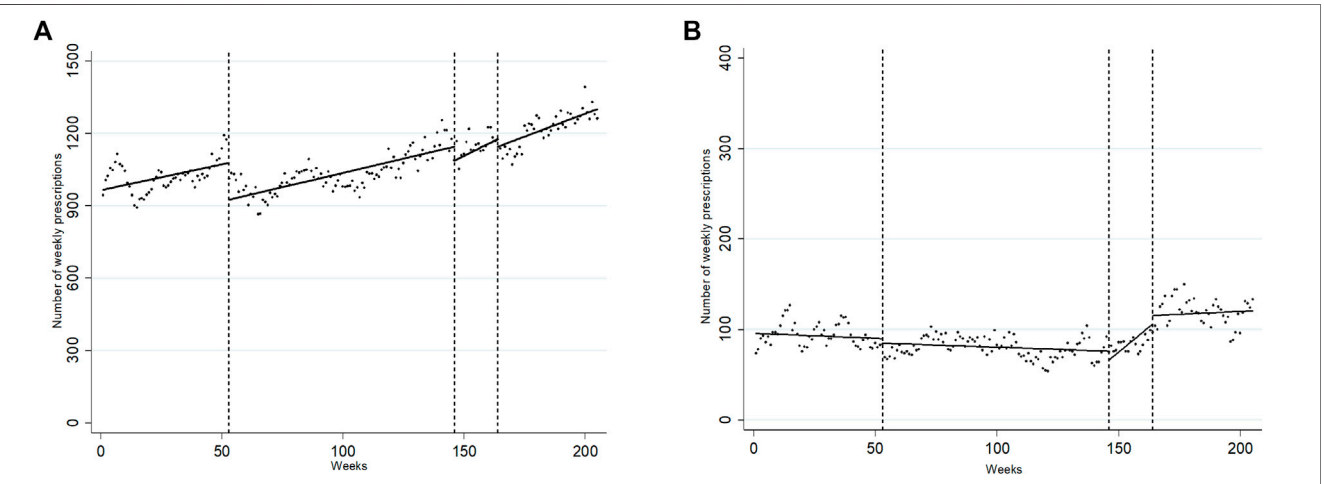


FIGURE 3 | Segmented linear regression trends of weekly series of IRF prescription for BCP in patients with chronic cancer pain treatment **(A)** and in patients without chronic cancer pain treatment **(B)**, 2015–2018. Dots: observed weekly volume of prescription; Line: predicted weekly volume of prescription. Week 0: first week of January 2015; Week 53: first medication review; Week 146: second medication review: Week 164: issue of safety warning. Week 205: last week of November 2018. Created by the authors.

TABLE 2 | Segmented regression parameters for IRF use for BCP with and without overlapping chronic cancer pain therapy.

Breakthrough cancer pain appropriate	**Coef.**	**Std. Err.**	**t**	**P>|t|**	**[95% conf**	**. Interval]**
Prev. slope	2.13	0.80	2.67	0.008	0.55	3.70
I1 (week 53)						
Level change	−152.26	25.18	−6.05	0.000	−201.93	−102.60
Slope change	0.23	1.00	0.23	0.822	−1.75	2.20
PI trend	2.35	0.44	5.34	0.000	1.48	3.25
I2 (week 146)						
Level change	−57.82	32.25	−1.79	0.075	−121.41	5.78
Slope change	2.63	3.08	0.86	0.393	−3.44	8.71
PI trend	4.989.151	2.890.009	1.73	0.086	−0.71	10.69
I3 (week 164)						
Level change	−31.98	32.95	−0.97	0.333	−96.96	33.01
Slope change	−1.18	3.50	−0.34	0.737	−8.07	5.72
PI trend	3.81	1.34	2.85	0.005	1.18	6.45
Constant	967.00	24.16	40.02	0.000	919.35	1014.64
Breakthrough Cancer Pain inappropriate	**Coef.**	**Std. Err.**	**t**	**P>|t|**	**[95% Conf**	**. Interval]**
Prev. slope	−0.11	0.21	−0.52	0.602	−0.53	0.31
I1 (week 53)						
Level change	−5.06	5.07	−1.00	0.319	−15.06	4.93
Slope change	0.02	0.24	0.07	0.942	−0.46	0.50
PI trend	−0.09	0.08	−1.17	0.242	−0.25	0.06
I2 (week 146)						
Level change	−10.10	3.91	−2.58	0.011	−17.82	−2.39
Slope change	2.32	0.64	3.63	0.000	1.06	3.57
PI trend	2.22	0.61	3.64	0.000	1.02	3.43
I3 (week 164)						
Level change	9.22	12.27	0.75	0.453	−14.97	33.41
Slope change	−2.09	0.77	−2.71	0.007	−3.61	−0.57
PI trend	0.13	0.40	0.33	0.740	−0.65	0.91
Constant	95.71	7.79	12.28	0.000	80.34	111.07
Durbin Watson statistic						
BCPa	2.137567					
BCPi	2.295185					

BCPi, potentially inappropriate breakthrough cancer pain in patients without overlapping chronic cancer pain therapy; BCPa, breakthrough cancer pain in patients with overlapping chronic pain therapy (appropriate); I1,I2, I3, first medication review, second medication review and national safety warning, respectively; PI trend, post-intervention trend.
Created by the authors.

followed an ascending trend thought the period. Even if this constitutes appropriate care in regulatory terms, this pattern of growth certainly calls for further attention. Immediate change levels for BCP use were observed after some of the interventions, but these should be interpreted with caution in terms of attribution due to several reasons. For instance, in the case of medication reviews, these are implemented gradually in the territory, and thus abrupt weekly changes should hardly be interpreted as a consequence of the interventions. Also, weekly series can be affected by unmeasured factors (such as holidays, or pharmacy accounting practices) that could translate into sudden changes in particular weeks. Finally, the rationale underlying these drug safety interventions should be to sustainedly improve medication use in the long term, therefore trends seem a more suitable outcome to assess their success than immediate level changes.

Many factors may explain the relative ineffectiveness of the interventions under assessment. In our setting, when a Safety Warning for the Spanish Agency for Medicines is issued, the regional health services passively disseminate this information to prescribers, usually *via* written letter or email. This strategy has

been proved to be ineffective to improve physician prescribing (Majumdar and Soumerai, 2003). The impact of regulatory safety warnings from regulatory bodies from Europe and the United States as well as for Spain has been evaluated in a few systematic reviews and studies that have provided mixed results, many of them showing no or modest effect. Even if their interpretation is hindered by the heterogeneity of the studies in terms of design, setting, outcomes analysed and methodological quality, there is a common recognition that many, multilevel and contextual factors may be mediating between the issue of warnings and their impact in clinical practice, such as for instance the very nature of the alert and the risks involved, the implementation of warning-related interventions by the health services, promotional activity or media coverage (Carracedo-Martínez and Pía-Morandeira, 2010; CarracedoMartínez and Pía-Morandeira, 2011; Carracedo-Martínez et al., 2012; Dusetzina et al., 2012; Piening et al., 2012; Carracedo-Martínez and Pia-Morandeira, 2016; Goedecke et al., 2018; Hurtado-Navarro et al., 2019; Georgi et al., 2020; Vázquez-Mourelle et al., 2020).

Medication review interventions that rely on active communication (as peer-comparison and audit) may impact prescribing, but only to a modest extent (Majumdar and Soumerai, 2003). In our case, they lead to modification or withdrawal of IRF treatment in about a third of patients treated with IRF. Among other potentially limiting factors such as prescriber unwillingness to comply with medication review recommendations, and despite the risks and controversies surrounding its use, there may still be clinical situations in acute NCP care (or exacerbated chronic NCP) where IRF may be a therapeutic choice to be considered, regardless of regulation. In this way, only partial effect may be reasonably expected. In our case, two apparently very similar medication review interventions seemed to have different impact in terms of intensity and duration. This inconclusive finding is aligned with international evidence on the effectiveness of opioid medication review interventions. In addition to the factors mentioned above, other qualitative and contextual mediating factors may also play an important explanatory role, such as individual commitment, leadership, interpersonal skills, political priority, financial incentives, etc (Gomes et al., 2014; Chang et al., 2016; Chang et al., 2018; Winstanley et al., 2018; Brighthaupt et al., 2019; Ranapurwala et al., 2019; Bhimji et al., 2020; Rao et al., 2020). Even so, multifaceted interventions designed with a strategic continuity over time and pursuing a sustained improvement of prescribing may prove more suitable to enable long-term prescription changes than isolated, one-component, one-off efforts (Majumdar and Soumerai, 2003; Huiskes et al., 2017).

This study has some limitations. First, the VID databases gather real-world clinical practice data and contain information as registered by health professionals during routine clinical practice, but data are not specifically prepared for research. In this sense, studies based on real-world clinical information like VID are at risk of well-known biases such a differential recording, misclassification bias or missing data. However, prescription and dispensation information (the essential data in this study) is of the highest quality, as it is used for billing purposes, and it includes paperless electronic prescription, the registration of any dispensation in any community pharmacy, and reimbursement to pharmacies in a traceable way for each pharmaceutical package and each patient. Second, although our analytic approach is considered one of the strongest non-experimental approaches for evaluating time-delimited interventions, we cannot rule out the possibility that the changes we observed were due to other events that occurred simultaneously with the interventions. However, we do not know of any other regional or national policies over the observation period that could have affected our results. Third, VID does not include data of inpatient medication, although consumption of IRF in this setting is expected to be marginal. Fourth, we did not employ a minimum daily-dosing criterion to define chronic cancer pain treatment, which could result in a slight mislabelling bias. Also, we only required 1 day of overlap to define appropriate IRF BCP prescription, which could result in a slight overestimation of appropriate prescription. However, this definition is commonly employed to define overlap in opioid-related real-world studies. Fifth, we did not investigate whether the interventions had an impact on the use of alternative treatments such as fast-release formulations of tapentadol or oxycodone. Sixth, we did not investigate whether the interventions had impact on the number of patients treated (see **Supplementary Material S2**), or on relevant clinical outcomes such as mortality, overdose or addiction. Finally, the generalization of our results to other settings outside Spain, or even to other Spanish regions, should be approached with great caution as contextual factors may play an important role in prescription patterns.

Our results call for a review of the design and implementation of policy interventions addressing IRF prescription quality. Even if the interventions showed modest, temporary, and uneven impact on prescription trends in noncancer pain, prescription of IRF decreased in the period 2015–2018. However, many signs indicate that the problem is far to be resolved. First, the increase of use in cancer pain and the sustained, potentially inappropriate use in a small group of patients with cancer call for attention. Second, in 2021 the country is the third largest consumer of fentanyl worldwide, only surpassed by Germany and the United States (International Narcotics C, 2021), and Valencia is the top consumer region of fentanyl in the country (among 17 regions, with a range of 3.80–1.70 DHD) (Ficheros de facturación and y Mutualidades., 2020) In this context and by the end of 2020, the VHS implemented a third medication review targeting IRF prescription, with a focus on reducing NCP prescription and long-term use of IRF for BCP, which entailed a modification of the electronic prescription system which now compels the prescriber to specify whether the prescription of IRF is "off-label." Finally, at a national level, a prior authorization scheme for IRF prescription entered into force in the country, 2021, by which every prescription gets to be validated by a so-called medical inspector before it is accepted for public funding and dispensing. In a context of contrasting reactions for and against the measure by primary care pharmacists (Prior Authorization Scheme for Immediate-Release Fentanyl:

Measures for an Uncontrolled Problem, 2021), patient associations and pain societies (Letter to the Ministry of Health about the Prior Authorization Scheme for Immediate-Release Fentanyl, 2021), these two latter interventions and their effect on the trends of use of IRF and related outcomes warrant further investigation.

ACCESS TO DATA

Legal restrictions on sharing the data set apply as regulated by the Valencia regional government by means of legal resolution by the Valencia Health Agency (2009/13312) which forbids the cession of data to third parties (accessible at: http://www.san.gva.es/documents/152919/157920/resolucionsolicituddatos.pdf). Upon request, authors can allow access to the databases in order to verify the accuracy of the analysis or the reproducibility of the study. Requests to access the datasets should be directed to Management Office of the Data Commission in the Valencia Health Agency (email: solicitud_datos@gva.es; telephone numbers: +34 961-928207; +34 961-928198).

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because legal restrictions on sharing the data set apply as regulated by the Valencia regional government by means of legal resolution by the Valencia Health Agency [2009/13312] which forbids the dissemination of data to third parties (accessible at: http://www.san.gva.es/documents/152919/157920/resolucionsolicituddatos.pdf). Upon request, authors can allow access to the databases in order to verify the accuracy of the analysis or the reproducibility of the study. Requests to access the datasets should be directed to Management Office of the Data Commission in the Valencia Health Agency (email: solicitud_datos@gva.es; telephone numbers: +34 961-928207; +34 961-928198) Requests to access the datasets should be directed to "solicitud_datos@gva.es".

ETHICS STATEMENT

The study was reviewed and approved by the Ethics Committee for Drug Research of the "Hospital Clínico-Universitario de Valencia" (Reference: F-CE-GeVA 14 v1.2; 2019, March 21). Written informed consent for participation was not required in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

IH, AG-S, SP, and GS were responsible for the study concept, design and data acquisition. IH carried out the data preparation and the statistical analysis and AG-S drafted the manuscript. IH, AG-S, SP, GS, FS, CR, MP, and ME participated in the analysis and interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version submitted for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.815719/full#supplementary-material

REFERENCES

Bhimji, H., Landry, E., and Jorgenson, D. (2020). Impact of Pharmacist-Led Medication Assessments on Opioid Utilization. *Can. Pharm. J. (Ott)* 153 (3), 148–152. Published 2020 Mar 13. doi:10.1177/1715163520908285

Bosetti, C., Santucci, C., Radrezza, S., Erthal, J., Berterame, S., and Corli, O. (2019). Trends in the Consumption of Opioids for the Treatment of Severe Pain in Europe, 1990-2016. *Eur. J. Pain* 23 (4), 697–707. doi:10.1002/ejp.1337

Bottomley, Christian., Scott, J., Anthony, G., and Isham, Valerie. (2019). Analysing Interrupted Time Series with a Control. *Epidemiologic Methods* 8 (1), 20180010. doi:10.1515/em-2018-0010

Brighthaupt, S. C., Stone, E. M., Rutkow, L., and McGinty, E. E. (2019). Effect of Pill Mill Laws on Opioid Overdose Deaths in Ohio & Tennessee: A Mixed-Methods Case Study. *Prev. Med.* 126, 105736. Epub 2019 May 29. PMID: 31152831. doi:10.1016/j.ypmed.2019.05.024

Carracedo Martínez, E., and Pía-Morandeira, A. (2011). Influence of a Regulatory Safety Warning on the Use of Telithromycin. *Med. Clin. (Barc)* 136 (10), 456–457. doi:10.1016/j.medcli.2009.07.026

Carracedo-Martínez, E., and Pia-Morandeira, A. (2016). Influence of Health Warnings on the Use of Rosiglitazone and Pioglitazone in an Area of Spain: A Time-Series Study, *SAGE Open Med*, 4. 2050312116653054. doi:10.1177/2050312116653054

Carracedo-Martínez, E., Pia-Morandeira, A., and Figueiras, A. (2012). Impact of a Health Safety Warning and Prior Authorisation on the Use of Piroxicam: a Time-Series Study. *Pharmacoepidemiol. Drug Saf.* 21 (3), 281–284. doi:10.1002/pds.2275

Carracedo-Martínez, E., and Pía-Morandeira, A. (2010). Impact of a Health Safety Warning on Strontium Ranelate Utilization. *Gac Sanit* 24 (2), 151–153. doi:10.1016/j.gaceta.2009.10.012

Chang, H. Y., Lyapustina, T., Rutkow, L., Daubresse, M., Richey, M., Faul, M., et al. (2016). Impact of Prescription Drug Monitoring Programs and Pill Mill Laws on High-Risk Opioid Prescribers: A Comparative Interrupted Time Series Analysis. *Drug Alcohol Depend* 165, 1–8. Epub 2016 Jun 2. doi:10.1016/j.drugalcdep.2016.04.033

Chang, H. Y., Murimi, I., Faul, M., Rutkow, L., and Alexander, G. C. (2018). Impact of Florida's Prescription Drug Monitoring Program and Pill Mill Law on High-Risk Patients: A Comparative Interrupted Time Series Analysis. *Pharmacoepidemiol. Drug Saf.* 27 (4), 422–429. Epub 2018 Feb 28. doi:10.1002/pds.4404

Dusetzina, S. B., Higashi, A. S., Dorsey, E. R., Conti, R., Huskamp, H. A., Zhu, S., et al. (2012). Impact of FDA Drug Risk Communications on Health Care Utilization and Health Behaviors: a Systematic Review. *Med. Care* 50, 466–478. doi:10.1097/MLR.0b013e318245a160

Ficheros de facturación, C. C. A. A., and y Mutualidades., I. N. E. (2020). *Población Padrón Municipal a 1 de enero de cada año*. Madrid: Ministerio de Sanidad. Noviembre.

García-Sempere, A., Orrico-Sánchez, A., Muñoz-Quiles, C., Hurtado, I., Peiró, S., Sanfélix-Gimeno, G., et al. (2020). Data Resource Profile: The Valencia Health System Integrated Database (VID). *Int. J. Epidemiol.* 49 (3), 740–741e. doi:10.1093/ije/dyz266

Georgi, U., Lämmel, J., Datzmann, T., Schmitt, J., and Deckert, S. (2020). Do drug-related Safety Warnings Have the Expected Impact on Drug Therapy? A Systematic Review. *Pharmacoepidemiol. Drug Saf.* 29 (3), 229–251. doi:10.1002/pds.4968

Goedecke, T., Morales, D. R., Pacurariu, A., and Kurz, X. (2018). Measuring the Impact of Medicines Regulatory Interventions - Systematic Review and Methodological Considerations. *Br. J. Clin. Pharmacol.* 84, 419–433. doi:10.1111/bcp.13469

Gomes, T., Juurlink, D., Yao, Z., Camacho, X., Paterson, J. M., Singh, S., et al. (2014). Impact of Legislation and a Prescription Monitoring Program on the Prevalence of Potentially Inappropriate Prescriptions for Monitored Drugs in Ontario: a Time Series Analysis. *CMAJ Open* 2 (4), E256–E261. doi:10.9778/cmajo.20140027

González-Bermejo, D., Rayón-Iglesias, P., Rodríguez-Pascual, A., Álvarez-Gutiérrez, A., Fernández-Dueñas, A., Montero-Corominas, D., et al. Drug Utilization Study on Immediate Release Fentanyl in Spain. Prevalence, Incidence, and Indication. *Pharmacoepidemiol. Drug Saf.* 2021 Mar;30(3): 371–378. doi:10.1002/pds.5118

González-Bermejo, D., Rayón-Iglesias, P., Rodríguez-Pascual, A., Álvarez-Gutiérrez, A., Fernández-Dueñas, A., Montero-Corominas, D., et al. (2021). Drug Utilization Study on Immediate Release Fentanyl in Spain. Prevalence, Incidence, and Indication. *Pharmacoepidemiol. Drug Saf.* 30 (3), 371–378.

Häuser, W., Buchser, E., Finn, D. P., Dom, G., Fors, E., Heiskanen, T., et al. Is Europe Also Facing an Opioid Crisis?-A Survey of European Pain Federation Chapters. *Eur. J. Pain*. 2021 Sep;25(8):1760–1769. doi:10.1002/ejp.1786

Hider-Mlynarz, K., Cavalié, P., and Maison, P. (2018). Trends in Analgesic Consumption in France over the Last 10 Years and Comparison of Patterns across Europe. *Br. J. Clin. Pharmacol.* 84, 1324–1334. doi:10.1111/bcp.13564

Huiskes, V. J., Burger, D. M., van den Ende, C. H., and van den Bemt, B. J. (2017). Effectiveness of Medication Review: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *BMC Fam. Pract.* 18 (1), 5. doi:10.1186/s12875-016-0577-x

Huitema, B. (2011). *The Analysis of Covariance and Alternative: Statistical Methods for Experiments, Quasi-Experiments, and Single-Case Studies*. 2nd ed. Hoboken, New Jersey: John Wiley & Sons, 367–402.Simple Interrupted Time-Series Designs.

Hurtado-Navarro, I., García-Sempere, A., Rodríguez-Bernal, C., Sanfélix-Genovés, J., Peiró, S., and Sanfélix-Gimeno, G. (2019). Impact of Drug Safety Warnings and Cost-Sharing Policies on Osteoporosis Drug Utilization in Spain: A Major Reduction but with the Persistence of over and Underuse. Data from the ESOSVAL Cohort from 2009 to 2015. *Front. Pharmacol.* 10, 768. doi:10.3389/fphar.2019.00768

Hurtado, I., García-Sempere, A., Peiró, S., and Sanfélix-Gimeno, G. (2020). Increasing Trends in Opioid Use from 2010 to 2018 in the Region of Valencia, Spain: A Real-World, Population-Based Study. *Front. Pharmacol.* 11, 612556. doi:10.3389/fphar.2020.612556

International Narcotics Control Board Estimated World Requirements of Narcotic Drugs in Grams for 2021 (August Update). Available at: https://www.incb.org/documents/Narcotic-Drugs/Status-of Estimates/2021/EstAug21_01092021.pdf (Accessed September 24, 2021).

Kobayashi, M. (1985). Comparison of Efficiencies of Several Estimators for Linear Regressions with Autocorrelated Errors. *J. Am. Stat. Assoc.* 80 (392), 951–953. doi:10.1080/01621459.1985.10478209

Letter to the Ministry of Health about the Prior Authorization Scheme for Immediate-Release Fentanyl. 2021. Spanish Federation of Patients and Spanish Multidisciplinar Society of Pain. Madrid. Available at: https://semdor.es/wp-content/uploads/2021/01/carta-transdisciplinar-FENTANILO-DE-LIBERACIO%CC%81N-RA%CC%81PIDA-v3.pdf (Accessed September 14, 2021).

Majumdar, S. R., and Soumerai, S. B. (2003). Why Most Interventions to Improve Physician Prescribing Do Not Seem to Work. *CMAJ* 169 (1), 30–31.

Piening, S., Haaijer-Ruskamp, F. M., de Vries, J. T., van der Elst, M. E., de Graeff, P. A., Straus, S. M., et al. (2012). Impact of Safety-Related Regulatory Action on Clinical Practice: a Systematic Review. *Drug Saf.* 35, 373–385. doi:10.2165/11599100-000000000-00000

Prior Authorization Scheme for Immediate-Release Fentanyl: Measures for an Uncontrolled Problem. Visado al Fentanilo de liberación rápida: medidas para problemas descontrolados. Spanish Society of Primary Care Pharmacists, 2021. Available at: https://www.sefap.org/2021/07/01/visado-al-fentanilo-de-liberacion-rapida/Accessed September 14, 2021.

Ranapurwala, S. I., Carnahan, R. M., Brown, G., Hinman, J., and Casteel, C. (2019). Impact of Iowa's Prescription Monitoring Program on Opioid Pain Reliever Prescribing Patterns: An Interrupted Time Series Study 2003-2014. *Pain Med.* 20 (2), 290–300. doi:10.1093/pm/pny029

Rao, T., Kiptanui, Z., Dowell, P., Triebwasser, C., Alexander, G. C., and Harris, I. (2020). Association of Formulary Exclusions and Restrictions for Opioid Alternatives with Opioid Prescribing Among Medicare Beneficiaries, *JAMA Netw. Open*, 3. 3, e200274. doi:10.1001/jamanetworkopen.2020.0274

Salazar, A., Moreno, S., De Sola, H., Moral-Munoz, J. A., Dueñas, M., and Failde, I. (2020). The Evolution of Opioid-Related Mortality and Potential Years of Life Lost in Spain from 2008 to 2017: Differences between Spain and the United States. *Curr. Med. Res. Opin.* 36 (2), 285–291. Epub 2019 Nov 6. doi:10.1080/03007995.2019.1684251

Spanish Agency of Medicines and Medical Devices (2021a). Fentanilo de liberación inmediata: importancia de respetar las condiciones de uso autorizadas. Available at: https://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano3/seguridad-1/2018/ni-muh_fv_5-2017-fentanilo/ (Accessed August 30).

Spanish Agency of Medicines and Medical Devices (2021b). Summary of Product Characteristics for Immediate Release Fentanyl. Spanish Agency of Medicines and Medical Devices. 371-378. Available at: https://cima.aemps.es/cima/dochtml/ft/70501/FT_70501.html (Accessed August 30).

U.S. Food and Drug Administration (2014). *Transmucosal Immediate Release Fentanyl Risk Evaluation and Mitigation Strategy*. Available at: https://www.fda.gov/media/82673/download (Accessed August 30, 2021).

Valencia Regional Government (2021). Conselleria de Sanidad Universal y Salud Pública. Programa REFAR-AR IV Gestor MI: Adecuación de los tratamientos de fentanilo de liberación rápida. Available at: http://www.san.gva.es/web/dgfps/-refar-programa-de-revision-y-seguimiento-de-la-farmacoterapiaAccessed August 31.

Vázquez-Mourelle, R., Carracedo-Martínez, E., and Figueiras, A. (2020). Impact of a Health Alert and its Implementation on Flutamide Prescriptions for Women: an Interrupted Time Series Analysis. *BMC Health Serv. Res.* 20, 597. doi:10.1186/s12913-020-05453-6

Winstanley, E. L., Zhang, Y., Mashni, R., Schnee, S., Penm, J., Boone, J., et al. (2018). Mandatory Review of a Prescription Drug Monitoring Program and Impact on Opioid and Benzodiazepine Dispensing. *Drug Alcohol Depend* 188, 169–174. Epub 2018 May 1. doi:10.1016/j.drugalcdep.2018.03.036

Zhu, W., Chernew, M. E., Sherry, T. B., and Maestas, N. (2019). Initial Opioid Prescriptions Among U.S. Commercially Insured Patients, 2012-2017. *N. Engl. J. Med.* 380 (11), 1043–1052. doi:10.1056/NEJMsa1807069

Conflict of Interest: Authors AG-S,IH,SP,FS-S,CLR-B and GS-S are employed by FISABIO, a research body in Spain affiliated with the Health Department of the Valencia Government. FISABIO signed a Collaboration agreement (2018-2019) with Grünenthal Pharma S.A., to conduct independent research on "Patterns of use of opioids in the National Health System", unrelated to the present work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 20 April 2022
doi: 10.3389/fphar.2022.871136

Trends of Utilization of Antiseizure Medications Among Pregnant Women in Manitoba, Canada: A 20-Year Population-Based Study

*Walid Shouman[1], Joseph A. Delaney[1,2], Kaarina Kowalec[1,3], Marcus Ng[4], Chelsea Ruth[4], Jamieson Falk[1], Christine Leong[1,5], Silvia Alessi-Severini[1], Alekhya Lavu[1], Payam Peymani[1] and Sherif Eltonsy[1,6]**

[1]College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [2]Department of Epidemiology, University of Washington, Seattle, WA, United States, [3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden, [4]College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [5]Department of Psychiatry, College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [6]Children's Hospital Research Institute of Manitoba, Winnipeg, MB, Canada

OPEN ACCESS

Edited by:
Andrea Burden,
ETH Zürich, Switzerland

Reviewed by:
Barbara Mostacci,
IRCCS Institute of Neurological Sciences of Bologna (ISNB), Italy
Dick Lindhout,
University Medical Center Utrecht, Netherlands

***Correspondence:**
Sherif Eltonsy
sherif.eltonsy@umanitoba.ca

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: 07 February 2022
Accepted: 14 March 2022
Published: 20 April 2022

Citation:
Shouman W, Delaney JA, Kowalec K, Ng M, Ruth C, Falk J, Leong C, Alessi-Severini S, Lavu A, Peymani P and Eltonsy S (2022) Trends of Utilization of Antiseizure Medications Among Pregnant Women in Manitoba, Canada: A 20-Year Population-Based Study. Front. Pharmacol. 13:871136. doi: 10.3389/fphar.2022.871136

Background: Evidence from developed countries demonstrates that the use of antiseizure medications (ASMs) has been increasing in the last decade. Pregnant women have a very challenging risk benefit trade-off in terms of ASM utilization, and it is crucial to know if increased utilization is seen among pregnant women.

Objective: To examine time-trends of utilization of ASM therapies among pregnant women in Manitoba, Canada.

Methods: We conducted a population-based cohort study using de-identified, linked administrative databases from Manitoba. Pregnancies between 1995 and 2018 were included. Four groups of pregnant people were created based on ASM exposure and epilepsy diagnosis.

Results: Of 273,492 pregnancies, 812 (3/1000) had epilepsy diagnosis and were exposed to ASMs, 963 (3.5/1000) had epilepsy diagnosis and were unexposed, and 2742 (10/1000) were exposed to ASMs and did not have epilepsy diagnosis. Overall, the number of pregnancies exposed to ASMs increased significantly from 0.56% in 1997 to 2.21% in 2018 ($p < 0.0001$). Subgroup analysis by epilepsy diagnosis showed no significant change in ASMs exposure among pregnant women with epilepsy [the proportion of women exposed to ASM from all pregnancies was 0.37% (in 1997) and 0.36% (in 2018), $p = 0.24$]. A drop in carbamazepine use was observed, while the number of lamotrigine prescriptions increased from 6.45% in 1997 to 52% by 2018. ASM use among pregnant women without epilepsy increased significantly from 0.19% in 1997 to 1.85% in 2018 ($p < 0.0001$). In the total cohort of pregnancies, 1439 (0.53%) were exposed during their entire pregnancy, and 1369 (0.5%) were exposed only in their first trimester. Clonazepam was the most used ASM during the study period (1953 users, 0.71%), followed by gabapentin (785 users, 0.29%) and carbamazepine (449 users, 0.16%).

Conclusion: No major shifts in the quantity of ASM use over the study period were observed among pregnant women with epilepsy. However, there was a significant increase in ASM use among pregnant women without epilepsy. The study results warrant further investigation into the implications of ASM use in pregnancy for indications other than epilepsy.

Keywords: utilization, pregnancy, antiepileptic, cohort, epilepsy

INTRODUCTION

The estimated prevalence of epilepsy among pregnant women ranges between 0.3 and 0.7% (Hauser et al., 1996; Whelehan and Delanty, 2019). Both epilepsy and antiseizure medications (ASMs) are associated with potential adverse effects to a pregnant person and their developing fetus (Pennell, 2016; Whelehan and Delanty, 2019). Pharmacological management with ASMs during pregnancy should be maintained at the lowest possible dose allowing for optimum seizure control and minimal fetal exposure (Patel and Pennell, 2016; Pennell, 2016). Worldwide, several studies have reported an increase in the use of ASMs for epilepsy and other indications such as neuropathic pain, other neurologic and psychiatric disorders, and movement disorders (restless leg syndrome) during pregnancy (Vajda et al., 2010; Kulaga et al., 2011; Bobo et al., 2012; Wen et al., 2015; Yeh et al., 2017; Kinney et al., 2018; Hurault-Delarue et al., 2019; Margulis et al., 2019; Cohen et al., 2020). In a recent study, the utilization trends of ASMs during pregnancy from five Nordic countries, the United States, and Australia were assessed between 2006 and 2016 (Cohen et al., 2020). A significant increase in the use of ASMs, particularly new generation ASMs such as lamotrigine, and a decrease in old generation ASMs such carbamazepine during pregnancy was found in all countries throughout the study period (Cohen et al., 2020). In Canada, a study from the province of Québec by Kulaga et al. (2011) found that the majority of pregnant women with epilepsy (79.6%) received ASM monotherapy, 5.8% received polytherapy, and 14.6% had no ASM exposure. Evidence shows that the adverse outcomes are dependent on the type of ASM used, the dose of fetal exposure at conception, and the trimester of exposure (Hill et al., 2010; Tomson and Battino, 2012; Pennell, 2016). Therefore, choosing the most appropriate ASM for women with epilepsy (WWE), with the lowest teratogenic risk is crucial (Hill et al., 2010; Tomson and Battino, 2012; Pennell, 2016).

In the Canadian province of Manitoba, evidence of an increase in ASM use among the general population exists (Leong et al., 2016). A study showed that ASM use increased significantly, from 8.3/1,000 to 23/1,000 between 1998 and 2013 (Leong et al., 2016). The study showed a 210% increase in ASM users with no epilepsy, and 55-fold increase in the use of gabapentin among users without epilepsy (Leong et al., 2016). The study, however, did not report subgroup analysis for the trends of utilization of ASMs in special populations, such as pregnant women (Leong et al., 2016). In the current study, we aim to examine the trends of utilization of ASMs during pregnancy and identify any changes in prescription patterns of ASM among pregnant people with epilepsy in Manitoba, Canada, between 1995 and 2019.

MATERIALS AND METHODS

Data Sources and Design

A retrospective population-based cohort study was conducted using de-identified data from the province of Manitoba, Canada. We constructed a cohort of all pregnant women in Manitoba from 1 January 1997 to 31 March 2019, using the administrative databases for the provincial healthcare system from the Manitoba Research Data Repository at the Manitoba Centre for Health Policy (MCHP), University of Manitoba. The database repository is a secure data-rich environment containing person-level health information on the entire population of Manitoba. All records in the repository are de-identified; however, records are linkable at the individual and family levels using a scrambled health number attached to each record. For the current study, we used the following linked databases: (1) The Manitoba Health Insurance Registry (date of birth, sex, comorbidities); (2) Drug Program Information Network (DPIN), which includes drug names, brand names, and dispensation dates and captures the dispensation of all prescription drugs by community pharmacies in Manitoba regardless of the insurance coverage type (1995/96–2018/19); (3) Hospital Discharge Abstracts, which include records of all patients' hospital admissions with summaries for demographic data (1992/93–2018/19), (4) Medical Services Database, which includes physician claims used to identify diagnosis codes using the International Classification of Diseases (ICD-9 and ICD-10) (1992/93–2018/19), (5) The Hospital Newborn to Mother Link, which serves to match the baby's birth hospital record with the mother's obstetrical delivery record, and (6) census data for income quintiles (IQ). All data sets were linked together using a scrambled personal health identification number that is unique for each mother (1995/96–2018/19). We conducted sensitivity analysis using diagnosis codes in 2, 5, and 10 years prior to pregnancy case. The 5 years' definition was used to minimize false-negative cases of epilepsy.

Study Population

We identified all pregnancies for women living in Manitoba between 1995 and 2018. A woman was considered to have epilepsy if she had ≥1 medical claims or ≥1 hospitalization for epilepsy during the 5 years prior to delivery (ICD-9: 345 or ICD-10: G40/G41) (Fisher et al., 2014; Tu et al., 2014; Leong

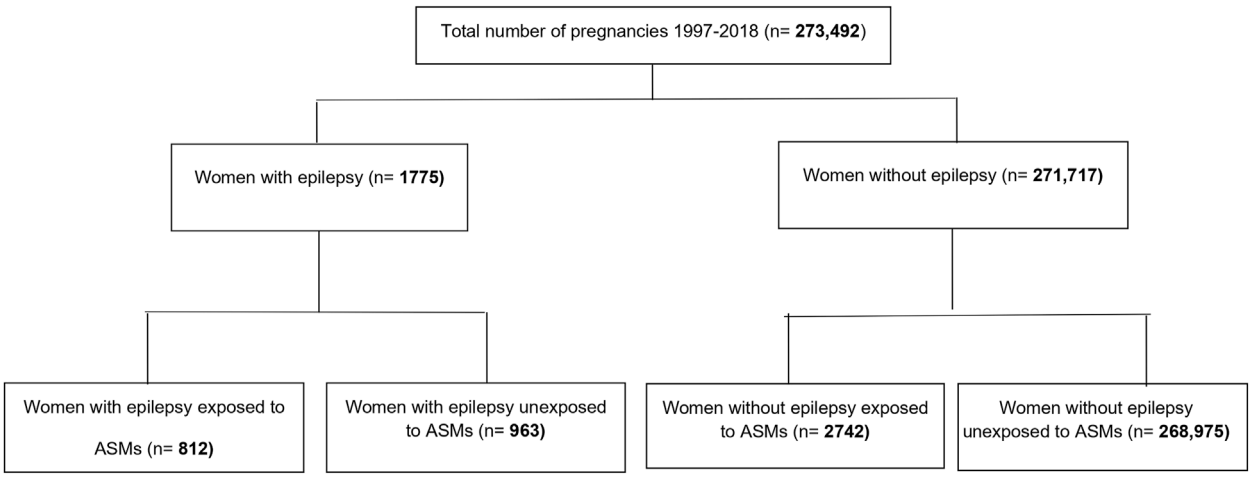


FIGURE 1 | Study flowchart.

et al., 2016). Four groups of pregnant women were created: (1) exposed pregnant women with epilepsy, (2) exposed pregnant women without epilepsy, (3) unexposed pregnant women with epilepsy, and (4) unexposed pregnant women without epilepsy. Women who did not have five-year coverage or whose children were born before 1 April 1997 were excluded due to <5 years of follow-up. The area of residence was defined as urban for women living in Winnipeg or Brandon or as rural for women living in all other areas of the province. Income quintiles were used to determine the socioeconomic status. Income quintile measures neighborhood socioeconomic status and divides the population into five income groups from the lowest to the highest income (approximately 20% of the population in each group) (Martens et al., 2015).

Exposure Definition

ASM utilization was identified using the Anatomical Therapeutic Chemical (ATC) codes. The exposure windows were first trimester (1st day of gestation–14th week), second trimester (15th week–25th week), third trimester (26th week–end of pregnancy), and anytime during pregnancy (1st day of gestation–end of pregnancy). Exposure to a prescribed ASM was defined as having ≥1 prescription filled during the exposure window of interest, or a prescription filled before the beginning of the exposure window but with a duration overlapping the exposure window. ASMs examined were identified using ATC codes within the prescription drug data, specifically all drugs coded as N03A for anti-epilepsy medication (**Supplementary Table S1**).

Statistical Analysis

The characteristics and comorbidities of women were evaluated using descriptive statistics. Patient comorbidities considered (including mood disorders, diabetes, and hypertension) are defined in **Supplementary Table S2**. The frequency and pattern of ASM use during the whole pregnancy and each trimester was estimated. The annual trend of use of ASMs was evaluated for the total study population and for women with epilepsy and women without epilepsy. Linear regression was used to model the annual trends of utilization of ASMs and specific ASMs in each group of pregnant women. Models were built using data from 1997 to 2018 as some medications were only available as of 1997. A p-value ≤0.05 was considered statistically significant. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

We identified 273,492 pregnancies, with a mean age of 28 years. Of these pregnancies, 0.3% (n = 812) were in women with epilepsy exposed to ASMs, 0.35% (n = 963) were pregnancies of women with epilepsy unexposed to ASM, and 1% (n = 2742) were women without epilepsy but exposed to ASMs (**Figure 1**). Among women with epilepsy, 31.3% (n = 254) of the exposed pregnancies and 31.3% (n = 301) of the unexposed pregnancies were in the lowest income quintile. Whereas, in women without epilepsy, 43.5% (n = 1193) of exposed pregnant women were in the lowest income quintile compared to 26.3% (n = 70812) in unexposed pregnant women (**Table 1**). Exposed pregnant women without epilepsy had higher rates of comorbidities compared to other groups. Among the exposed pregnant women without epilepsy, 65.21% were diagnosed with anxiety and 20.31% were diagnosed with pain when compared to 10.22 and 5.55%, respectively, in unexposed pregnant women without epilepsy (**Table 1**).

Linear regression analyses showed the number of pregnancies exposed to ASMs increased significantly from 0.56% in 1997 to 2.21% in 2018 (p < 0.0001) (**Figure 2**). There was no significant change in the percentage of

TABLE 1 | Characteristics of the study population by group.

		Exposed		Unexposed	
		Pregnant women with epilepsy	Pregnant women without epilepsy	Pregnant women with epilepsy	Pregnant women without epilepsy
Total, N (%)		812 (0.3%)	2,742 (1%)	963 (0.4%)	268,975 (98.4%)
Mean age (SD)		27.9 (±5.5)	29.2 (±5.6)	26.6 (±6)	28.1 (±5.8)
SES quartiles	1 (Lowest)	254 (31.3%)	1193 (43.5%)	301 (31.3%)	70812 (26.3%)
	2	214 (26.4%)	561 (20.5%)	203 (21.1%)	56928 (21.2%)
	3	153 (18.8%)	434 (15.8%)	196 (20.4%)	49153 (18.3%)
	4	110 (13.6%)	286 (10.4%)	166 (17.2%)	49483 (18.4%)
	5 (Highest)	75 (9.2%)	258 (9.4%)	95 (9.9%)	41820 (15.6%)
Area of residence	Rural	357 (44.0%)	1029 (37.5%)	387 (40.2%)	125655 (46.7%)
	Urban	449 (55.3%)	1703 (62.1%)	574 (59.6%)	142541 (53.0%)
Hypertension, N (%)		27 (3.3%)	227 (8.3%)	34 (3.5%)	4212 (1.5%)
Diabetes, N (%)		26 (3.2%)	212 (7.7%)	34 (3.5%)	7684 (2.9%)
Mood and anxiety disorders, N (%)		189 (23.3%)	1788 (65.2%)	208 (21.6%)	27481 (10.2%)
Schizophrenia, N (%)		10 (1.2%)	90 (3.3%)	suppressed	583 (0.2%)
Personality disorder, N (%)		34 (4.2%)	270 (9.9%)	38 (4.0%)	2638 (1.0%)
Pain, N (%)		86 (10.6%)	557 (20.3%)	122 (12.7%)	14932 (5.6%)
Birth status	Stillborn, N (%)	Suppressed	28 (1.0%)	8 (0.8%)	8 (0.8%)
	Singleton, N (%)	788 (97.0%)	2666 (97.2%)	945 (98.1%)	262111 (97.5%)
	Multiple births, N (%)	24 (3.0%)	76 (2.8%)	18 (1.9%)	6864 (2.6%)

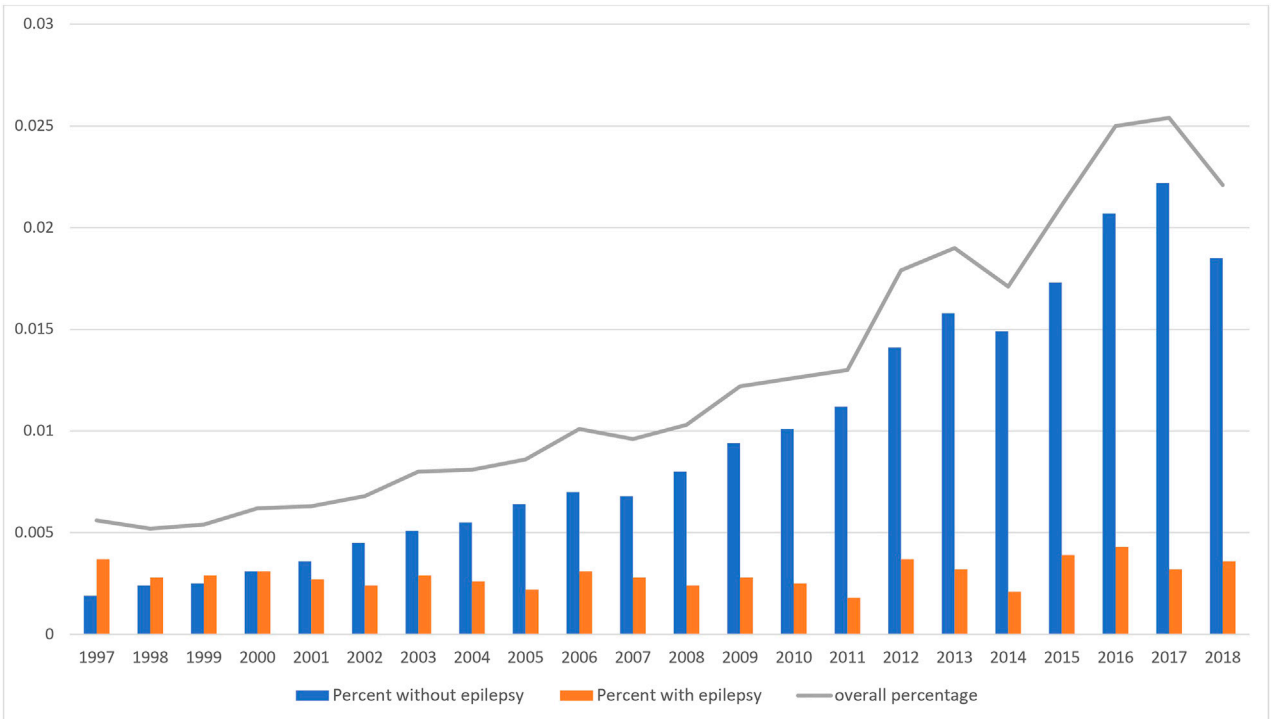


FIGURE 2 | Annual Trend of utilization of ASMs among all pregnant women with and without epilepsy.

pregnant women with epilepsy exposed to ASMs from 0.37% in 1997 to 0.36% in 2018 (p = 0.2354), while the percentage of ASM-exposures among pregnant women without epilepsy increased significantly (0.19% in 1997 to 1.85% in 2018, p < 0.0001) (**Figure 2**).

Trimester Analysis

Trimester analysis showed 0.53% (n = 1439) of women were exposed throughout their pregnancy, 0.5% (n = 1369) were exposed only in the first trimester, 0.02% (n = 63) were exposed only during the second trimester, and 0.07% (n =

TABLE 2 | Percentage of exposed pregnancies to each ASM by group.

	All exposed pregnant women (%)	Exposed pregnant women with epilepsy (%)	Exposed pregnant women without epilepsy
Clonazepam	45.88	6.19	59.67%
Gabapentin	18.38	3.6	23.52%
Carbamazepine	9.33	28.07	2.81%
Lamotrigine	7.86	18.88	4.03%
Levetiracetam	1.31	4.9	Suppressed
Valproic acid	5.46	10.79	3.61%
Phenytoin	5.44	17.08	1.39%
Topiramate	4.41	6.39	3.72%

Values ≤5 were suppressed.

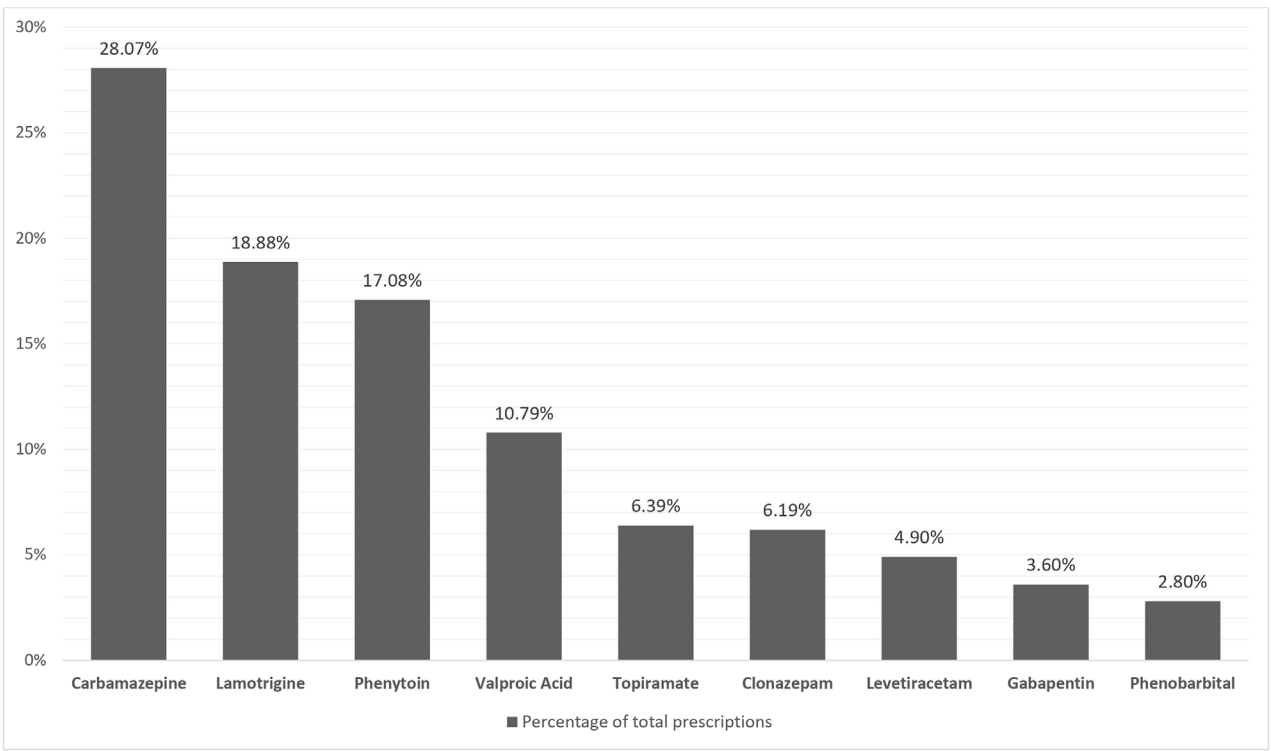


FIGURE 3 | Most used ASMs among pregnant women with epilepsy.

184) were exposed only during the third trimester. Among women with epilepsy, 33.58% were exposed throughout the pregnancy. Detailed analysis of exposures by trimester is presented in **Supplementary Figures S1–S3**.

The most used ASM among pregnant women with and without epilepsy, throughout the study period was clonazepam (44.44% of all exposed pregnancies) followed by gabapentin (17.85%) and carbamazepine (10.22%) (**Table 2**). Whereas, among pregnant women with epilepsy, carbamazepine (33.86%), lamotrigine (22.77%), phenytoin (17.08%), and valproic acid (13%) were the most used (**Figure 3**).

At the start of the study period, carbamazepine was the most prescribed ASM for pregnant women with epilepsy (51%), however, this decreased to 12.5% in 2018, whereas the number of lamotrigine prescriptions increased from 6.45% (1997) to 52% (2018) (**Figure 4**). On the other hand, among women without epilepsy, clonazepam remained the most used ASM throughout the study period. However, its utilization decreased from 88.2% in 1997 to 47.97% in 2018. Gabapentin first appeared among women without epilepsy in 2001 and its utilization increased to reach 40.2% of prescriptions in 2018 (**Figure 5**).

DISCUSSION

In this population-based cohort study, we observed a significant increase in the utilization of ASMs among pregnant women in the Canadian province of Manitoba between 1997 and 2018. This increase

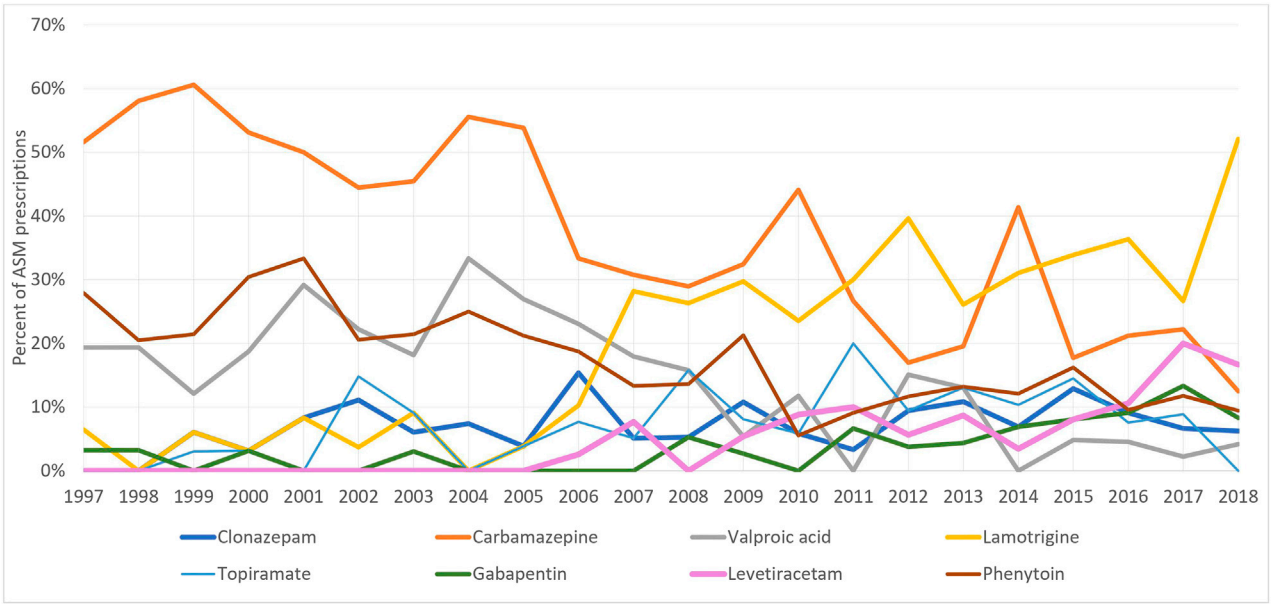


FIGURE 4 | Trends of top ASM prescriptions among pregnant women with epilepsy.

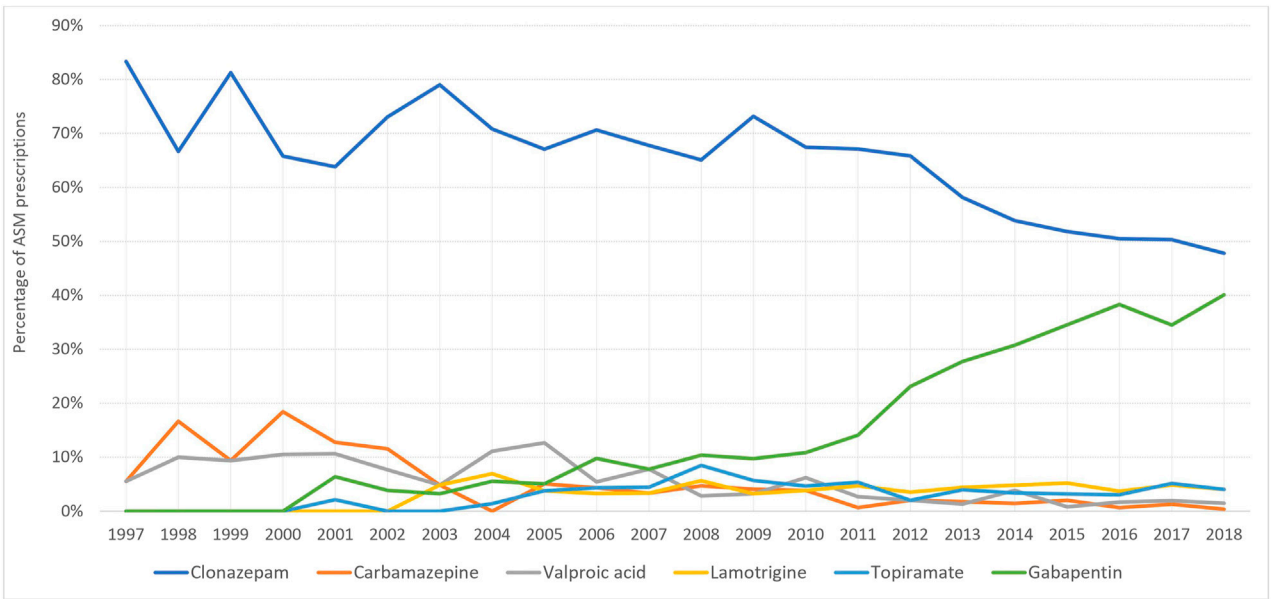


FIGURE 5 | Trends of top ASM prescriptions among pregnant women without epilepsy.

was attributed mainly to the increased use of clonazepam and gabapentin among pregnant women without epilepsy. In general, there was no major shift in the utilization of ASMs among pregnant women with epilepsy over the study. By contrast, a significant increase in the utilization of ASMs among pregnant women without epilepsy was observed. Our study showed an increase in lamotrigine prescriptions among pregnant women with epilepsy and a decrease in valproic acid and carbamazepine use. Similar results were reported in the United Kingdom and Ireland, with an increase in lamotrigine and levetiracetam use and a decrease in valproic acid and carbamazepine between 1996 and 2016 (Kinney et al., 2018). Lamotrigine prescriptions increased from 15% of the total ASM prescriptions in the United Kingdom and Ireland in 2000 to 31% in 2016, while at the same time, valproic acid prescriptions decreased from 22% in 2000 to less than 5% in 2016 (Kinney et al., 2018). ASMs are frequently used for indications other than seizure

control (LiverTox, 2012; Dokkedal-Silva et al., 2019). For example, valproic acid has been indicated for bipolar disorder and schizophrenia (LiverTox, 2012; Dokkedal-Silva et al., 2019). Lamotrigine has been indicated in bipolar depression in adults (Goldenberg, 2010). Gabapentin is primarily used to treat neuropathic pain, namely, trigeminal neuralgia, HIV-associated neuralgia, diabetic neuropathy, and neoplasia (Magnus, 1999; Goldenberg, 2010). It is also used in the treatment of psychiatric disorders, most notably bipolar disorder, and in movement disorders such as restless leg syndrome (Magnus, 1999; Goldenberg, 2010). Most exposed pregnant women with epilepsy (33.6%) were exposed throughout their pregnancy period, and while the main reasons are unknown, this could be a reflection to optimal management of seizures by practitioners. Among the pregnant women with epilepsy, >54% were unexposed to any ASM, this could be attributed to the presence of mild/non–medication-controlled epilepsy, or a potential misclassification of epilepsy definition used in our study (for example, isolated seizures not related to epilepsy).

Strengths and Limitations

The databases used in this study are a major strength in terms of size and coverage, and the validity and reliability of the MCHP Repository for epidemiological studies has been previously reported (Leong et al., 2016; Azimaee et al., 2018). The MCHP repository includes medical records for all Manitoba residents recorded in the process of routine care. Our study captured the prescription practices of prescribers in Manitoba during the past 20 years. Our study, however, has limitations. First, exposure was derived from dispensing records and not actual intake (Azimaee et al., 2018). Second, we did not have data on the severity of epilepsy cases. Finally, since many prescriptions started prior to pregnancy, a proportion of women may have stopped taking their medications as soon as they become pregnant, without a database record, thus overestimating some ASMs exposures.

CONCLUSION

Over the study period, no major shifts in the overall use of ASMs were observed among pregnant women with epilepsy. The reduction in carbamazepine and valproic acid use coupled with the increase in lamotrigine and levetiracetam use reflects Manitoba prescribers' adherence to updated guidelines (CCSO, 2015). Consistent with previous reports among the general population of Manitoba, gabapentin is increasingly used among pregnant women, mostly for non-epilepsy indications. Future studies on the utilization and safety outcomes of gabapentin and other new-generation ASMs in pregnancy, as well as studies focusing on pre-pregnancy counseling and management are warranted to inform prescribers and policymakers.

DATA AVAILABILITY STATEMENT

The data sets presented in this article are not readily available because data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba, and were derived from data provided by Manitoba Health. Requests to access the data sets should be directed to Manitoba Centre for Health Policy, https://umanitoba.ca/manitoba-centre-for-health-policy/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Health Research Ethics Board (HREB) at the University of Manitoba and Manitoba Health Information Privacy Committee (HIPC). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors contributed to the concept and design of the study. WS was responsible for the analysis and drafted the first draft of the manuscript. All authors contributed to drafting and revising of the full manuscript and have approved the manuscript as submitted. All authors have met the criteria of authorship and take public responsibility for the manuscript contents.

FUNDING

The study was funded through awards from the Manitoba Medical Services Foundation, Winnipeg Foundation, and Health Sciences Centre Foundation to cover data analysis, stipends, and publication fees.

ACKNOWLEDGMENTS

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project #H2020:088 (HS23673) (HIPC#2019/2020-60). The results and conclusions are those of the authors, and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba, and were derived from data provided by Manitoba Health and Manitoba Health Insurance Registry, Drug Program Information Network, Hospital Discharge, and Medical Services database.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.871136/full#supplementary-material

REFERENCES

Azimaee, M., Smith, M., Lix, L., Ostapyk, T., and Burchill, C. (2018). *MCHP Data Quality Framework*. Winnipeg, Manitoba, Canada: Manitoba Centre for Health Policy, University of Manitoba.

Bobo, W. V., Davis, R. L., Toh, S., Li, D. K., Andrade, S. E., Cheetham, T. C., et al. (2012). Trends in the Use of Antiepileptic Drugs Among Pregnant Women in the US, 2001-2007: a Medication Exposure in Pregnancy Risk Evaluation Program Study. *Paediatr. Perinat. Epidemiol.* 26, 578–588. doi:10.1111/ppe.12004

CCSO (2015). Provincial Guidelines for the Management of Epilepsy in Adults and Children. Available from: www.ontarioepilepsyguidelines.ca (Accessed December 11, 2021).

Cohen, J. M., Cesta, C. E., Furu, K., Einarsdóttir, K., Gissler, M., Havard, A., et al. (2020). Prevalence Trends and Individual Patterns of Antiepileptic Drug Use in Pregnancy 2006-2016: A Study in the Five Nordic Countries, United States, and Australia. *Pharmacoepidemiol. Drug Saf.* 29, 913–922. doi:10.1002/pds.5035

Dokkedal-Silva, V., Berro, L. F., Galduróz, J. C. F., Tufik, S., and Andersen, M. L. (2019). Clonazepam: Indications, Side Effects, and Potential for Nonmedical Use. *Harv. Rev. Psychiatry* 27, 279–289. doi:10.1097/HRP.0000000000000227

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., et al. (2014). ILAE Official Report: a Practical Clinical Definition of Epilepsy. *Epilepsia* 55, 475–482. doi:10.1111/epi.12550

Goldenberg, M. M. (2010). Overview of Drugs Used for Epilepsy and Seizures: Etiology, Diagnosis, and Treatment. *P T* 35, 392–415.

Hauser, W. A., Annegers, J. F., and Rocca, W. A. (1996). Descriptive Epidemiology of Epilepsy: Contributions of Population-Based Studies from Rochester, Minnesota. *Mayo Clin. Proc.* 71, 576–586. doi:10.4065/71.6.576

Hill, D. S., Wlodarczyk, B. J., Palacios, A. M., and Finnell, R. H. (2010). Teratogenic Effects of Antiepileptic Drugs. *Expert Rev. Neurother.* 10, 943–959. doi:10.1586/ern.10.57

Hurault-Delarue, C., Morris, J. K., Charlton, R., Gini, R., Loane, M., Pierini, A., et al. (2019). Prescription of Antiepileptic Medicines Including Valproate in Pregnant Women: A Study in Three European Countries. *Pharmacoepidemiol. Drug Saf.* 28, 1510–1518. doi:10.1002/pds.4897

Kinney, M. O., Morrow, J., Patterson, C. C., Campbell, E., Russell, A., Smithson, H. W., et al. (2018). Changing Antiepilepsy Drug-Prescribing Trends in Women with Epilepsy in the UK and Ireland and the Impact on Major Congenital Malformations. *J. Neurol. Neurosurg. Psychiatry* 89, 1320–1323. doi:10.1136/jnnp-2017-317368

Kulaga, S., Sheehy, O., Zargarzadeh, A. H., Moussally, K., and Bérard, A. (2011). Antiepileptic Drug Use during Pregnancy: Perinatal Outcomes. *Seizure* 20, 667–672. doi:10.1016/j.seizure.2011.06.012

Leong, C., Mamdani, M. M., Gomes, T., Juurlink, D. N., Macdonald, E. M., and Yogendran, M. (2016). Antiepileptic Use for Epilepsy and Nonepilepsy Disorders: A Population-Based Study (1998-2013). *Neurology* 86, 939–946. doi:10.1212/WNL.0000000000002446

LiverTox. Valproate - LiverTox - NCBI Bookshelf. 2012 Available from: https://www.ncbi.nlm.nih.gov/books/NBK548284/table/Valproate.Td/

Magnus, L. (1999). Nonepileptic Uses of Gabapentin. *Epilepsia* 40 (Suppl. 6), S66–S72. doi:10.1111/j.1528-1157.1999.tb00936.x

Margulis, A. V., Hernandez-Diaz, S., McElrath, T., Rothman, K. J., Plana, E., Almqvist, C., et al. (2019). Relation of In-Utero Exposure to Antiepileptic Drugs to Pregnancy Duration and Size at Birth. *PLoS One* 14, e0214180. doi:10.1371/journal.pone.0214180

Martens, P. J., Nickel, N., Forget, E., Lix, L., Turner, D., Prior, H., et al. (2015). *The Cost of Smoking in Manitoba*. Winnipeg MB: Manitoba Centre for Health Policy.

Patel, S. I., and Pennell, P. B. (2016). Management of Epilepsy during Pregnancy: an Update. *Ther. Adv. Neurol. Disord.* 9, 118–129. doi:10.1177/1756285615623934

Pennell, P. B. (2016). Use of Antiepileptic Drugs during Pregnancy: Evolving Concepts. *Neurotherapeutics* 13, 811–820. doi:10.1007/s13311-016-0464-0

Tomson, T., and Battino, D. (2012). Teratogenic Effects of Antiepileptic Drugs. *Lancet Neurol.* 11, 803–813. doi:10.1016/S1474-4422(12)70103-5

Tu, K., Wang, M., Jaakkimainen, R. L., Butt, D., Ivers, N. M., Young, J., et al. (2014). Assessing the Validity of Using Administrative Data to Identify Patients with Epilepsy. *Epilepsia* 55, 335–343. doi:10.1111/epi.12506

Vajda, F. J., Hollingworth, S., Graham, J., Hitchcock, A. A., O'Brien, T. J., Lander, C. M., et al. (2010). Changing Patterns of Antiepileptic Drug Use in Pregnant Australian Women. *Acta Neurol. Scand.* 121, 89–93. doi:10.1111/j.1600-0404.2009.01260.x

Wen, X., Meador, K. J., and Hartzema, A. (2015). Antiepileptic Drug Use by Pregnant Women Enrolled in Florida Medicaid. *Neurology* 84, 944–950. doi:10.1212/WNL.0000000000001304

Whelehan, A., and Delanty, N. (2019). Therapeutic Strategies for Treating Epilepsy during Pregnancy. *Expert Opin. Pharmacother.* 20, 323–332. doi:10.1080/14656566.2018.1550073

Yeh, C. C., Lussier, E. C., Sun, Y. T., Lan, T. Y., Yu, H. Y., and Chang, T. Y. (2017). Antiepileptic Drug Use Among Women from the Taiwanese Registry of Epilepsy and Pregnancy: Obstetric Complications and Fetal Malformation Outcomes. *PLoS One* 12, e0189497. doi:10.1371/journal.pone.0189497

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 20 April 2022
doi: 10.3389/fphar.2022.861953

The Risk of Ventricular Dysrhythmia or Sudden Death in Patients Receiving Serotonin Reuptake Inhibitors With Methadone: A Population-Based Study

Tony Antoniou[1,2,3,4]*, *Daniel McCormack*[4], *Mina Tadrous*[4,5,6], *David N. Juurlink*[4,7,8] and *Tara Gomes*[2,4,5,9]

[1]Department of Family and Community Medicine, Unity Health Toronto, Toronto, ON, Canada, [2]Li Ka Shing Knowledge Institute, Unity Health Toronto, Toronto, ON, Canada, [3]Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada, [4]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada, [5]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada, [6]Women's College Research Institute, Toronto, ON, Canada, [7]Sunnybrook Research Institute, Toronto, ON, Canada, [8]Department of Medicine, University of Toronto, Toronto, ON, Canada, [9]Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

OPEN ACCESS

Edited by:
Andrea Burden,
ETH Zürich, Switzerland

Reviewed by:
Bert Vandenberk,
University of Calgary, Canada
Geoffrey Isbister,
The University of Newcastle, Australia
Mehrul Hasnain,
Independent researcher, Mount Pearl, NL, Canada

***Correspondence:**
Tony Antoniou
Tony.Antoniou@unityhealth.to

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: 25 January 2022
Accepted: 11 March 2022
Published: 20 April 2022

Citation:
Antoniou T, McCormack D, Tadrous M, Juurlink DN and Gomes T (2022) The Risk of Ventricular Dysrhythmia or Sudden Death in Patients Receiving Serotonin Reuptake Inhibitors With Methadone: A Population-Based Study. Front. Pharmacol. 13:861953. doi: 10.3389/fphar.2022.861953

Background: Methadone is associated with ventricular dysrhythmias and sudden death. Serotonin reuptake inhibitors (SRIs) may increase the risk of these events either by inhibiting metabolism of methadone's proarrhythmic (S)-enantiomer, additive QT interval prolongation, or both. We sought to determine whether certain SRIs were associated with a higher risk of methadone-related ventricular dysrhythmias or sudden death.

Methods: We conducted a nested case-control study of Ontario residents receiving methadone between April 1, 1996 and December 31, 2017. Cases, defined as patients who died of sudden cardiac death or were hospitalized with a ventricular dysrhythmia while on methadone, were matched with up to four controls who also received methadone on age, sex, and a disease risk score. We determined the odds ratio (OR) and *p*-value functions for the association between methadone-related cardiotoxicity and treatment with SRIs known to inhibit metabolism of (S)-methadone (paroxetine, fluvoxamine, sertraline) or prolong the QT interval (citalopram and escitalopram). Patients who were not treated with an SRI served as the reference group.

Results: During the study period, we identified 626 cases and 2,299 matched controls. Following multivariable adjustment, we found that recent use of sertraline, fluvoxamine or paroxetine (adjusted OR 1.30; 95% confidence intervals [CI] 0.90–1.86) and citalopram and escitalopram (adjusted OR 1.26; 95% CI 0.97–1.63) were associated with small increases in the risk methadone-related cardiac toxicity, an assertion supported by the corresponding *p*-value functions.

Interpretation: Certain SRIs may be associated with a small increase in cardiac toxicity in methadone-treated patients.

Keywords: methadone, serotonin reuptake inhibitor, nested case control studies, sudden cardiac arrest, pharmacoepidemiogy

INTRODUCTION

Methadone is a long-acting opioid used primarily as treatment for opioid use disorder (Bell and Strang, 2020). However, methadone maintenance therapy can be complicated by QT interval prolongation in up to 50% of patients (Fanoe et al., 2007; Anchersen et al., 2009; Fareed et al., 2013; Chowdhury et al., 2015; Titus-Lay et al., 2021), with case reports and pharmacovigilance data describing the potential for ensuing Torsade de Pointes and sudden cardiac death (Chugh et al., 2008; Stringer et al., 2009; Kao et al., 2013; Kao et al., 2015). Risk factors for QT interval prolongation and sudden cardiac death are well described, and include older age, female sex, electrolyte abnormalities, and underlying heart disease (Chugh, 2010; Tisdale et al., 2013; Trinkley et al., 2013).

Drug interactions are another important and potentially avoidable risk factor for ventricular dysrhythmias in patients receiving methadone (Stringer et al., 2009). Because co-occurring mental health illness is common in methadone-treated patients and serotonin reuptake inhibitors (SRIs) are the most commonly prescribed class of antidepressants, the likelihood of co-prescription and potential interaction with methadone is high (Callaly et al., 2001; Rosen et al., 2008; Audi et al., 2018; Kane, 2021). However, SRIs differ in their propensity for causing drug interactions because of variable effects on drug metabolizing cytochrome P450 (CYP) isoenzymes as well as the QT interval (Hemeryck and Belpaire, 2002; Beach et al., 2014). This is especially relevant in the case of methadone, which is commercially available as a racemic mixture containing equal amounts of the (R)- and (S)-methadone enantiomers, each of which has distinct clinical and pharmacokinetic properties (Chang et al., 2011). Specifically (R)-methadone is an opioid agonist while (S)-methadone is associated with QT prolongation, increasing the risk of ventricular dysrhythmia and sudden death (Kristensen et al., 1995; Eap et al., 2007; Ansermot et al., 2010). Importantly, each enantiomer is metabolized by different CYP450 enzymes, with the CYP2B6 isoenzyme demonstrating stereoselectivity toward (S)-methadone (Chang et al., 2011; Dobrinas et al., 2013). Concomitantly administered medications that inhibit CYP2B6 may increase (S)-methadone concentrations and therefore increase the risks of dysrhythmia and sudden death. Among SRIs, prior studies have found that fluvoxamine and paroxetine increase concentrations of (S)-methadone by 30–50%, with no such increase observed with fluoxetine (Eap et al., 1997; Begré et al., 2002). In a study of 16 patients receiving methadone, sertraline, which inhibits CYP2B6, was also found to increase methadone levels by 26% (Hamilton et al., 2000). In addition to pharmacokinetic interactions, methadone-related dysrhythmia and sudden death can occur with the concurrent use of additional QT-prolonging drugs. Among SRIs, citalopram and escitalopram are associated with greater QT prolongation and a higher risk of sudden cardiac death than other agents (Castro et al., 2013; Beach et al., 2014; Assimon et al., 2019). The potential for a clinically important interaction between citalopram and methadone was highlighted by a study of forensic toxicological records in the United States, in which a strong signal for drug fatality with combined use was detected (Saad et al., 2018).

However, despite these data, the cardiac safety of combining SRIs with methadone is unknown. We sought to characterize the risk of ventricular dysrhythmias and sudden death in patients receiving these drug combinations in clinical practice. We speculated that, owing to pharmacokinetic and pharmacodynamic interactions, patients treated with methadone and either sertraline, paroxetine, fluvoxamine, citalopram or escitalopram would be at higher risk of these events relative to patients who were not prescribed SRIs.

MATERIALS AND METHODS

Setting

We conducted a nested case-control study of Ontario residents treated with publicly funded methadone maintenance therapy between 1 April 1996 and 31 December 2017. These individuals had universal access to hospital care, physicians' services, and prescription drug coverage.

Data Sources

We identified prescription records using the Ontario Drug Benefit (ODB) Database, which contains comprehensive records of prescription medications dispensed to Ontario residents whose prescriptions costs are reimbursed by the provincial government. Approximately 70% of methadone-treated patients in Ontario obtain their medication through the ODB program. Methadone prescriptions are recorded in the ODB database for each date on which the drug is dispensed. We obtained hospitalization and emergency department visit data from the Canadian Institute for Health Information Discharge Abstract Database and National Ambulatory Care Reporting System, respectively. We used the Ontario Health Insurance Plan database to identify claims for physician services and used validated disease registries to define the presence of diabetes (Hux et al., 2002), hypertension (Tu et al., 2007), and congestive heart failure (Schultz et al., 2013). We obtained basic demographic data from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. We ascertained sudden death using the Ontario Registrar General Death database, which contains the cause of death reported on individual death certificates. These datasets were linked using unique encoded identifiers, analyzed at ICES, and are routinely used to study the consequences of drug interactions (Antoniou et al., 2015; Gomes et al., 2017).

Study Subjects

We defined case patients as those who died of sudden cardiac death or were hospitalized with ventricular dysrhythmia or cardiac arrest (see **Supplementary Table 1** for International Classification of Disease and Related Health Problems, ninth and 10th revision codes) on the day of or within 1 day after receiving a prescription for methadone. Previous studies evaluating the accuracy of these codes show positive predictive

values exceeding 80% (De Bruin et al., 2005; Chung et al., 2010; Tamariz et al., 2012; Qirjazi et al., 2016).

We defined the index date as the date of death or hospitalization, with only the first instance of hospitalization considered for patients with more than one admission during the study period. In cases where individuals had multiple methadone claims on a given day, we assumed that the individual was exposed to methadone for the number of days corresponding to the number of claims. For example, an individual with three methadone claims on a Monday was assumed to be exposed to methadone until Wednesday and could become a case patient if they experienced sudden cardiac death or ventricular dysrhythmia on any day between Monday and Thursday (i.e., within 1 day of methadone exposure). The index date for potential controls was randomly assigned according to the distribution of index dates for included cases. For each case, we selected up to four controls from the same cohort of patients receiving methadone who were alive on their randomly selected index date. We excluded individuals with a prior diagnosis of cardiac arrest or dysrhythmia within 5 years of the index date and individuals receiving palliative care in the 6 months preceding the index date. We also excluded patients (i.e., <5 cases, 70 controls) who filled prescriptions for multiple SRIs in the 90 days preceding the index date to avoid the potential confounding effects of multiple SRI exposures. We required that all study patients have at least one methadone prescription on their index date or the day preceding it, and at least 6 months of continuous eligibility for public drug benefits prior to their index date.

To increase the comparability of cases and controls, we used a disease risk score as a confounder summary score to generate predicted probabilities of sudden cardiac death or ventricular dysrhythmia (Arbogast et al., 2008). We selected this approach because of the large number of potential confounders relative to the number of events and to attempt to balance the determinants of our outcome and baseline outcome risk among cases and controls. The disease risk score was derived for each individual using a non-parsimonious multivariable logistic regression model that included our study outcome as the dependent variable and an extensive list of demographic and clinical characteristics related to the risk of this outcome (**Supplementary Material**—Covariates Included in Disease Risk Score). We matched each case with up to four controls on their disease risk score (within 0.2 standard deviations), age (within 3 years), and sex. When fewer than four control subjects were available for each case, we analyzed only those controls and maintained the matching process. We excluded cases that could not be matched to at least one control.

Exposure to SRIs

For each case patient we identified prescriptions for one of citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline in the 90 days preceding the index date. We excluded fluoxetine because of the small number of cases exposed to this drug (n = 17).

Statistical Analysis

We used standardized differences to compare baseline characteristics of cases and controls. Standardized differences of less than 0.1 indicate good balance between cases and controls for a given covariate (Austin et al., 2007).

We quantified the association between SRIs and cardiac toxicity in methadone-treated patients using two approaches. First, we used conditional logistic regression to estimate the odds ratio and 95% confidence intervals for the association between sudden cardiac death or ventricular dysrhythmia and receipt of a prescription for an SRI anticipated to increase the risk of these outcomes through either a pharmacokinetic (paroxetine, fluvoxamine, sertraline) or pharmacodynamic (citalopram and escitalopram) interaction with methadone. Patients not treated with an SRI served as the reference group. We adjusted all models for baseline variables with a standardized difference exceeding 0.1. Next, we constructed *p*-value functions to graphically convey the strength and precision of the relationship between SRIs and cardiac events among methadone-treated patients (Infanger and Schmidt-Trucksäss, 2019; Rothman et al., 2021). Because *p*-value functions display point estimates, one-sided and two-sided confidence limits at any level, and one-sided and two-sided *p* values for any null and non-null value in a single graph, they are more informative than single *p*-values or confidence intervals when presenting study findings (Infanger and Schmidt-Trucksäss, 2019; Rothman et al., 2021). Moreover, *p*–value functions provide an estimate of the counter-null value—the point estimate supported by the same amount of evidence as the null value of no effect—thereby discouraging dichotomization of results as "significant" or "non-significant" when drawing inferences (Greenland, 2017; Laber and Shedden, 2017; Infanger and Schmidt-Trucksäss, 2019; Rothman et al., 2021). Analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, North Carolina) and R Studio.

RESULTS

During the 21-year study period, we identified 960,933 patients who died of sudden cardiac death or were hospitalized with ventricular dysrhythmia. After exclusions, 670 of these individuals had been prescribed methadone within 1 day of death or hospitalization. Of the 670 patients, 626 (93.4%) were matched to at least one control. Overall, baseline characteristics of cases and controls were well balanced, with mean ages of 46.0 years (standard deviation ±11.6) and 45.3 years (standard deviation ±11.3), respectively (**Table 1**). As expected, case patients exhibited greater co-morbidity, received more prescription drugs in the preceding year, and had more visits with a cardiologist in the preceding year (**Table 1**).

Following multivariable adjustment, we found that use of sertraline, fluvoxamine or paroxetine (adjusted OR 1.30; 95% CI 0.90–1.86) was associated with a slightly increased risk of cardiac toxicity during methadone therapy (**Table 2**). The point estimate, representing the value most compatible with the observed data, is displayed at the peak of the corresponding *p*-value function (**Figure 1**). Importantly, the point estimate and a considerable portion of the

TABLE 1 | Characteristics of cases and controls.

Variable	Cases (n = 626)	Controls (n = 2,299)	Standardized difference[a]
Age (median, IQR)	47 (37–55)	46 (36–54)	0.06
18–34	16 (2.6%)	63 (2.7%)	0.01
35–44	113 (18.1%)	441 (19.2%)	0.03
45–64	141 (22.5%)	534 (23.2%)	0.02
65–74	198 (31.6%)	739 (32.1%)	0.01
75+	158 (25.2%)	522 (22.7%)	0.06
Female, No. (%)	227 (36.3%)	863 (37.5%)	0.03
Cardiologist visits in preceding year (median, IQR)	0 (0–1)	0 (0–1)	0.19
Charlson Co-morbidity Index, No. (%)			
No hospitalization	324 (51.8%)	1,266 (55.1%)	0.07
0	127 (20.3%)	523 (22.7%)	0.06
1	83 (13.3%)	267 (11.6%)	0.05
2 +	92 (14.7%)	243 (10.6%)	0.12
History of congestive heart failure, No. (%)	38 (6.1%)	80 (3.5%)	0.12
History of angina, No. (%)	17 (2.7%)	36 (1.6%)	0.08
History of acute myocardial infarction, No. (%)	34 (5.4%)	89 (3.9%)	0.07
History of hypertension, No. (%)	193 (30.8%)	616 (26.8%)	0.09
History of chronic kidney disease (3 years), No. (%)	16 (2.6%)	41 (1.8%)	0.05
Diabetes, No. (%)	112 (17.9%)	360 (15.7%)	0.06
Atherosclerotic disease, No. (%)	33 (5.3%)	90 (3.9%)	0.06
Stroke, No. (%)	12 (1.9%)	30 (1.3%)	0.05
Cardiomyopathy, No. (%)	6 (1.0%)	10 (0.4%)	0.06
Alcohol use disorder (3 years), No. (%)	54 (8.6%)	145 (6.3%)	0.09
Chronic liver disease (3 years), No. (%)	36 (5.8%)	89 (3.9%)	0.09
Residence in a long-term care facility, No. (%)	≤5[b]	≤5[b]	0.05
Number of prescription drugs in previous year, (median, IQR)	11 (7–16)	11 (6–15)	0.09
Medication use in preceding 120 days, No. (%)			
Non-potassium sparing diuretics	102 (16.3%)	282 (12.3%)	0.12
Potassium sparing diuretics[b]	6 (1.0%)	12 (0.5%)	0.05
Beta adrenergic receptor antagonists	58 (9.3%)	166 (7.2%)	0.07
ACE inhibitors	84 (13.4%)	258 (11.2%)	0.07
Angiotensin II receptor antagonists	21 (3.4%)	85 (3.7%)	0.02
Spironolactone	27 (4.3%)	54 (2.3%)	0.11
Potassium supplements	≤5[b]	≤5[b]	0.04
Direct renin inhibitors	0 (0%)	0 (0%)	0
Calcium channel blockers	61 (9.7%)	184 (8.0%)	0.06
Digoxin	≤5[b]	≤5[b]	0.01
Antiarrhythmic drugs	0 (0%)	≤5[b]	0.03
Nitrates	17 (2.7%)	38 (1.7%)	0.07
Anticoagulants	20 (3.2%)	46 (2.0%)	0.08
Antiplatelet drugs	16 (2.6%)	37 (1.6%)	0.07
Aspirin	190 (30.4%)	752 (32.7%)	0.05
Statins	68 (10.9%)	217 (9.4%)	0.05
Fibrates	≤5[b]	≤5[b]	0.01
Oral hypoglycemics	46 (7.3%)	158 (6.9%)	0.02
Insulin	37 (5.9%)	110 (4.8%)	0.05
Antipsychotic agents	170 (27.2%)	631 (27.4%)	0.01
Non-SRI antidepressants	200 (31.9%)	713 (31.0%)	0.02
Tricyclic antidepressants	88 (14.1%)	321 (14.0%)	0.00
Prokinetics	19 (3.0%)	78 (3.4%)	0.02
Opioids	176 (28.1%)	659 (28.7%)	0.01
Sedative-hypnotics	228 (36.4%)	866 (37.7%)	0.03
Cholinesterase inhibitors	≤5[b]	≤5[b]	0.02
Procedures in preceding 5 years No. (%)			
Coronary artery bypass graft	≤5[b]	10 (0.4%)	0.01
Angiography	36 (5.8%)	93 (4.0%)	0.08
Percutaneous transluminal coronary angioplasty	18 (2.9%)	39 (1.7%)	0.08
Permanent pacemaker insertion	0 (0.0%)	≤5[b]	0.05
Valve surgery	≤5[b]	15 (0.7%)	0.02
Carotid endartectomy	0 (0.0%)	0 (0.0%)	0.00
Echocardiography	209 (33.4%)	665 (28.9%)	0.10
Electrocardiography	540 (86.3%)	1967 (85.6%)	0.02
Holter monitor	54 (8.6%)	164 (7.1%)	0.06
Nuclear medicine stress test	32 (5.1%)	74 (3.2%)	0.09
Carotid Doppler ultrasonography	27 (4.3%)	73 (3.2%)	0.06

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of cases and controls.

Variable	Cases (n = 626)	Controls (n = 2,299)	Standardized difference[a]
Income Quintile, No. (%)			
1 (lowest)	304 (48.6%)	1,105 (48.1%)	0.01
2	146 (23.3%)	549 (23.9%)	0.01
3	81 (12.9%)	294 (12.8%)	0
4	58 (9.3%)	229 (10.0%)	0.02
5	37 (5.9%)	122 (5.3%)	0.03

[a]*Difference between cases and controls divided by standard deviation.*
[b]*Non-spironolactone potassium-sparing diuretics; prevalence not reported because of small cell size.*

TABLE 2 | Association between sudden death or ventricular dysrhythmia and recent serotonin reuptake inhibitor use.

Serotonin Reuptake Inhibitor (SRI) Exposure in Preceding 90 days[a]	Patients		Odds ratio (95%confidence Interval)	Adjusted odds ratio† (95% confidence Interval)
	Cases (n = 626)	Controls (n = 2,299)		
	No. (%)	No. (%)		
Paroxetine/fluvoxamine/sertraline	44 (7.0%)	132 (5.7%)	1.30 (0.91–1.86)	1.30 (0.90–1.86)
Citalopram/escitalopram	93 (14.9%)	285 (12.4%)	1.24 (0.96–1.60)	1.26 (0.97–1.63)
No SRI	489 (78.1%)	1,882 (81.9%)	1.00	1.00

[a]*Reference group: no SRI, use.*
†Adjusted for congestive heart failure, spironolactone, non-potassium sparing diuretics, number of cardiologist visits and drug claims in preceding year, echocardiography in preceding 5 years.

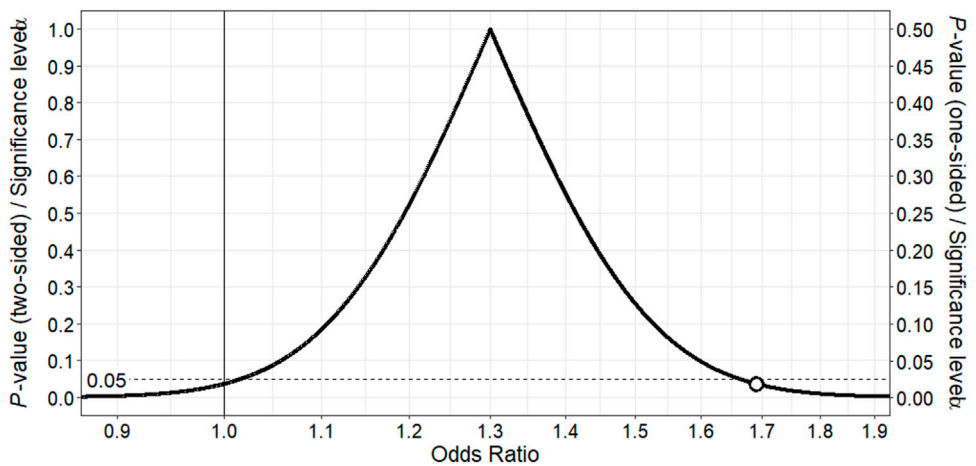


FIGURE 1 | *p*-value function for odds ratio for association between fluvoxamine, paroxetine or sertraline and ventricular dysrhythmia or sudden death in methadone-treated patients. The point estimate of 1.30 corresponds to the peak of the *p*-value function. The vertical continuous line denotes the null value for the odds ratio, and the white point the counter-null value of 1.69, which is the effect size supported by the same amount of evidence as the null value.

range of effect values consistent with the data exceed 1, supporting an imprecise yet slightly higher risk of cardiac toxicity with these SRIs among methadone-treated patients relative to patients not treated with SRIs. Moreover, the counter-null value is 1.69, demonstrating that a 69% increase in the risk of cardiac toxicity is supported by the same amount of evidence as an odds ratio of 1.0.

Similarly, use of citalopram or escitalopram therapy was associated with a modestly higher risk of cardiac events (adjusted OR 1.26; 95% CI 0.97–1.63) relative to no SRI therapy (**Table 2**). The point estimate and most of the corresponding *p*-value function lie above 1, providing support for a slightly higher risk of cardiac toxicity with these SRIs in methadone-treated patients relative to no SRI therapy (**Figure 2**). The counter-null value is 1.59, demonstrating that a 59% increased risk in cardiac toxicity is supported by the same amount of evidence as a null finding of no risk.

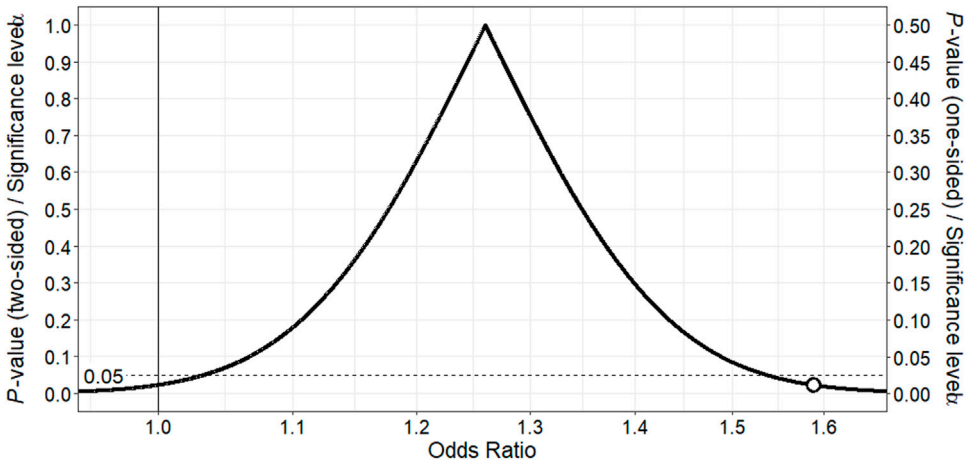


FIGURE 2 | *p*-value function for odds ratio for association between citalopram or escitalopram and ventricular dysrhythmia or sudden death in methadone-treated patients.The point estimate of 1.26 corresponds to the peak of the *p*-value function. The vertical continuous line denotes the null value for the odds ratio, and the white point the counter-null value of 1.59, which is the effect size supported by the same amount of evidence as the null value.

INTERPRETATION

In this population-based study, we found that use of SRIs known to increase levels of (S)-methadone or prolong the QT interval were associated with a slight increase in the risk of dysrhythmias or sudden cardiac death in methadone-treated patients, an assertion supported by the individual point estimates and shapes of the corresponding *p*-value functions. Although the magnitude of the effect size is small, our findings support the existence of a potentially life-threatening drug interaction between methadone and certain SRIs in clinical practice.

Our findings build upon earlier research exploring interactions between SRIs and methadone. Specifically, past studies have found that fluvoxamine and paroxetine increase concentrations of (S)-methadone (Eap et al., 1997; Begré et al., 2002), and that this enantiomer is 3.5-times more potent than (R)-methadone in blocking the voltage-gated potassium channel of the human ether-a-*go-go* related gene (hERG) (Eap et al., 2007). Similarly, prior research demonstrating that sertraline inhibits CYP2B6 and that individuals with the slow metabolizer phenotype of CYP2B6 have higher (S)-methadone concentrations and longer QT intervals than individuals with normal CYP2B6 activity supports the notion of a clinically important interaction between methadone and sertraline (Hamilton et al., 2000). Because the QT interval has been found to increase by 19.2 s for every 1,000 ng/ml increase in (S)-methadone concentrations (Csajka et al., 2016), accumulation of this enantiomer following the co-administration of sertraline, fluvoxamine or paroxetine provides a reasonable mechanistic basis for the increased risk of cardiac toxicity with combined use. The finding of a higher risk of methadone-related cardiac toxicity with citalopram and escitalopram aligns with the known QT prolonging effects of these drugs (Castro et al., 2013; Beach et al., 2014). While this effect is likely of minimal significance in patients with no other risk factors for dysrhythmias, it may contribute to life-threatening QT interval prolongation in patients receiving concurrent therapy with proarrhythmic drugs such as methadone. Moreover, the combination of methadone and citalopram was invariably fatal in an exploratory study of drug combinations associated with opioid deaths, lending additional support to the notion of an important pharmacodynamic interaction between these drugs (Saad et al., 2018).

Our findings have important implications for public health. Methadone remains a cornerstone of therapy for the management of opioid use disorder, with the World Health Organization classifying it as an essential medication in 2005 (Herget, 2005). However, methadone-related QT interval prolongation and ventricular dysrhythmia are important contributors to methadone-related morbidity and mortality. Importantly, a community-based study of 22 cases of methadone-related sudden cardiac death at therapeutic doses identified an anatomical cardiac cause in only 23% of cases, with no clear cause identified for the remaining patients (Chugh et al., 2008). In contrast, a cardiac cause could be identified for 60% of non-methadone-related cases of sudden cardiac death. Although the overall risk of torsades de pointes is small and associated with multiple risk factors, our findings highlight an underappreciated drug interaction between methadone and commonly prescribed SRIs as a potential component cause in the occurrence of methadone-related cardiac toxicity, particularly among patients with no pre-existing cardiac risk factors for dysrhythmia. In light of our findings and past research, clinicians should follow standard methadone monitoring practices to mitigate the risk combined methadone-SRI therapy, including identification and management of risk factors for ventricular dysrhythmias, pre-treatment and follow-up electrocardiographic monitoring, and if clinically appropriate, selection of an antidepressant that does not interact with methadone.

Our study has some limitations. First, we used administrative data, and had no access to serum electrolytes, electrocardiograms, treatment adherence, and use of non-prescribed medications. Although we used validated codes for our outcomes,

misclassification is possible. However, these limitations apply equally to all SRIs. Second, our study population comprised individuals eligible for public drug coverage in Ontario, which accounts for 70% of all methadone-treated patients in the province. Consequently, our findings may not be generalizable to all methadone-treated patients. Third, we were unable to reliably determine methadone dose. However, a dose-response relationship for methadone-related cardiotoxicity has not been clearly established, with cardiac effects documented at therapeutic doses (Chugh et al., 2008; Roy et al., 2012; Isbister et al., 2017). Fourth, some imbalance in baseline characteristics was apparent between cases and controls despite matching on a disease risk index. However, this is expected in case-control studies when cases are defined by an adverse outcome, and our analysis was adjusted for imbalanced variables. Finally, as with all observational studies, confounding due to unmeasured variables is a potential source of bias.

In conclusion, we found that SRIs expected to increase concentrations of the cardiotoxic (S)-methadone enantiomer or prolong the QT interval were associated with ventricular dysrhythmia and sudden cardiac death in patients receiving methadone. When combined therapy is required, the risks of a drug interaction can be minimized through careful patient selection that considers additional risk factors for QT prolongation and increased patient monitoring.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data set from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access (available at www.ices.on.ca/DAS). Requests to access these datasets should be directed to; www.ices.on.ca/DAS.

AUTHOR CONTRIBUTIONS

TA, DM, MT, DJ, and TG contributed to conception and design of the study. DM performed the statistical analysis. TA wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOH or MLTC is intended or should be inferred. Tara Gomes holds a Canada Research Chair in Drug Policy Research and Evaluation.

ACKNOWLEDGMENTS

We thank IQVIA Solutions Canada Inc. for use of their Drug Information File. Parts of this material are based on data and information compiled and provided by the Ontario Ministry of Health and CIHI. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Adapted from Statistics Canada, Postal Code Conversion File, 2016. This does not constitute an endorsement by Statistics Canada of this product. Parts of this report are based on Ontario Registrar General (ORG) information on deaths, the original source of which is ServiceOntario. The views expressed therein are those of the author and do not necessarily reflect those of ORG or the Ministry of Government and Consumer Services.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.861953/full#supplementary-material.

REFERENCES

Anchersen, K., Clausen, T., Gossop, M., Hansteen, V., and Waal, H. (2009). Prevalence and Clinical Relevance of Corrected QT Interval Prolongation during Methadone and Buprenorphine Treatment: a Mortality Assessment Study. *Addiction* 104, 993–999. doi:10.1111/j.1360-0443.2009.02549.x

Ansermot, N., Albayrak, O., Schläpfer, J., Crettol, S., Croquette-Krokar, M., Bourquin, M., et al. (2010). Substitution of (R,S)-methadone by (R)-methadone: Impact on QTc Interval. *Arch. Intern. Med.* 170, 529–536. doi:10.1001/archinternmed.2010.26

Antoniou, T., Hollands, S., Macdonald, E. M., Gomes, T., Mamdani, M. M., and Juurlink, D. N.Canadian Drug Safety; Effectiveness Research Network (2015). Trimethoprim-sulfamethoxazole and Risk of Sudden Death Among Patients Taking Spironolactone. *CMAJ* 187, E138–E143. doi:10.1503/cmaj.140816

Arbogast, P. G., Kaltenbach, L., Ding, H., and Ray, W. A. (2008). Adjustment for Multiple Cardiovascular Risk Factors Using a Summary Risk Score. *Epidemiology* 19, 30–37. doi:10.1097/EDE.0b013e31815be000

Assimon, M. M., Brookhart, M. A., and Flythe, J. E. (2019). Comparative Cardiac Safety of Selective Serotonin Reuptake Inhibitors Among Individuals Receiving Maintenance Hemodialysis. *J. Am. Soc. Nephrol.* 30, 611–623. doi:10.1681/ASN.2018101032

Audi, S., Burrage, D. R., Lonsdale, D. O., Pontefract, S., Coleman, J. J., Hitchings, A. W., et al. (2018). The 'top 100' Drugs and Classes in England: an Updated 'starter Formulary' for Trainee Prescribers. *Br. J. Clin. Pharmacol.* 84, 2562–2571. doi:10.1111/bcp.13709

Austin, P. C., Grootendorst, P., and Anderson, G. M. (2007). A Comparison of the Ability of Different Propensity Score Models to Balance Measured Variables between Treated and Untreated Subjects: a Monte Carlo Study. *Stat. Med.* 26, 734–753. doi:10.1002/sim.2580

Beach, S. R., Kostis, W. J., Celano, C. M., Januzzi, J. L., Ruskin, J. N., Noseworthy, P. A., et al. (2014). Meta-analysis of Selective Serotonin Reuptake Inhibitor-Associated QTc Prolongation. *J. Clin. Psychiatry* 75, e441–9. doi:10.4088/JCP.13r08672

Begré, S., von Bardeleben, U., Ladewig, D., Jaquet-Rochat, S., Cosendai-Savary, L., Golay, K. P., et al. (2002). Paroxetine Increases Steady-State Concentrations of (R)-methadone in CYP2D6 Extensive but Not Poor Metabolizers. *J. Clin. Psychopharmacol.* 22, 211–215. doi:10.1097/00004714-200204000-00017

Bell, J., and Strang, J. (2020). Medication Treatment of Opioid Use Disorder. *Biol. Psychiatry* 87, 82–88. doi:10.1016/j.biopsych.2019.06.020

Callaly, T., Trauer, T., Munro, L., and Whelan, G. (2001). Prevalence of Psychiatric Disorder in a Methadone Maintenance Population. *Aust. N. Z. J. Psychiatry* 35, 601–605. doi:10.1080/0004867010060507

Castro, V. M., Clements, C. C., Murphy, S. N., Gainer, V. S., Fava, M., Weilburg, J. B., et al. (2013). QT Interval and Antidepressant Use: A Cross Sectional Study of Electronic Health Records. *BMJ* 346, f288. doi:10.1136/bmj.f288

Chang, Y., Fang, W. B., Lin, S. N., and Moody, D. E. (2011). Stereo-Selective Metabolism of Methadone by Human Liver Microsomes and cDNA-Expressed Cytochrome P450s: a Reconciliation. *Basic Clin. Pharmacol. Toxicol.* 108, 55–62. doi:10.1111/j.1742-7843.2010.00628.x

Chowdhury, M., Wong, J., Cheng, A., Khilkin, M., and Palma, E. (2015). Methadone Therapy in Underserved Urban Community: QTc Prolongation and Life-Threatening Ventricular Arrhythmias. *Cardiovasc. Ther.* 33, 127–133. doi:10.1111/1755-5922.12120

Chugh, S. S. (2010). Early Identification of Risk Factors for Sudden Cardiac Death. *Nat. Rev. Cardiol.* 7, 318–326. doi:10.1038/nrcardio.2010.52

Chugh, S. S., Socoteanu, C., Reinier, K., Waltz, J., Jui, J., and Gunson, K. (2008). A Community-Based Evaluation of Sudden Death Associated with Therapeutic Levels of Methadone. *Am. J. Med.* 121, 66–71. doi:10.1016/j.amjmed.2007.10.009

Chung, C. P., Murray, K. T., Stein, C. M., Hall, K., and Ray, W. A. (2010). A Computer Case Definition for Sudden Cardiac Death. *Pharmacoepidemiol. Drug Saf.* 19, 563–572. doi:10.1002/pds.1888

Csajka, C., Crettol, S., Guidi, M., and Eap, C. B. (2016). Population Genetic-Based Pharmacokinetic Modeling of Methadone and its Relationship with the QTc Interval in Opioid-Dependent Patients. *Clin. Pharmacokinet.* 55, 1521–1533. doi:10.1007/s40262-016-0415-2

De Bruin, M. L., van Hemel, N. M., Leufkens, H. G., and Hoes, A. W. (2005). Hospital Discharge Diagnoses of Ventricular Arrhythmias and Cardiac Arrest Were Useful for Epidemiologic Research. *J. Clin. Epidemiol.* 58, 1325–1329. doi:10.1016/j.jclinepi.2005.04.009

Dobrinas, M., Crettol, S., Oneda, B., Lahyani, R., Rotger, M., Choong, E., et al. (2013). Contribution of CYP2B6 Alleles in Explaining Extreme (S)-Methadone Plasma Levels: a CYP2B6 Gene Resequencing Study. *Pharmacogenet Genomics* 23, 84–93. doi:10.1097/FPC.0b013e32835cb2e2

Eap, C. B., Bertschy, G., Powell, K., and Baumann, P. (1997). Fluvoxamine and Fluoxetine Do Not Interact in the Same Way with the Metabolism of the Enantiomers of Methadone. *J. Clin. Psychopharmacol.* 17, 113–117. doi:10.1097/00004714-199704000-00010

Eap, C. B., Crettol, S., Rougier, J. S., Schläpfer, J., Sintra Grilo, L., Déglon, J. J., et al. (2007). Stereoselective Block of hERG Channel by (S)-Methadone and QT Interval Prolongation in CYP2B6 Slow Metabolizers. *Clin. Pharmacol. Ther.* 81, 719–728. doi:10.1038/sj.clpt.6100120

Fanoe, S., Hvidt, C., Ege, P., and Jensen, G. B. (2007). Syncope and QT Prolongation Among Patients Treated with Methadone for Heroin Dependence in the City of Copenhagen. *Heart* 93, 1051–1055. doi:10.1136/hrt.2006.100180

Fareed, A., Vayalapalli, S., Scheinberg, K., Gale, R., Casarella, J., and Drexler, K. (2013). QTc Interval Prolongation for Patients in Methadone Maintenance Treatment: a Five Years Follow-Up Study. *Am. J. Drug Alcohol. Abuse* 39, 235–240. doi:10.3109/00952990.2013.804525

Gomes, T., Juurlink, D. N., Antoniou, T., Mamdani, M. M., Paterson, J. M., and van den Brink, W. (2017). Gabapentin, Opioids, and the Risk of Opioid-Related Death: A Population-Based Nested Case-Control Study. *Plos Med.* 14, e1002396. doi:10.1371/journal.pmed.1002396

Greenland, S. (2017). Invited Commentary: The Need for Cognitive Science in Methodology. *Am. J. Epidemiol.* 186, 639–645. doi:10.1093/aje/kwx259

Hamilton, S. P., Nunes, E. V., Janal, M., and Weber, L. (2000). The Effect of Sertraline on Methadone Plasma Levels in Methadone-Maintenance Patients. *Am. J. Addict* 9, 63–69. doi:10.1080/10550490050172236

Hemeryck, A., and Belpaire, F. M. (2002). Selective Serotonin Reuptake Inhibitors and Cytochrome P-450 Mediated Drug-Drug Interactions: an Update. *Curr. Drug Metab.* 3, 13–37. doi:10.2174/1389200023338017

Herget, G. (2005). Methadone and Buprenorphine Added to the WHO List of Essential Medicines. *HIV AIDS Pol. L. Rev* 10, 23–24.

Hux, J. E., Ivis, F., Flintoft, V., and Bica, A. (2002). Diabetes in Ontario: Determination of Prevalence and Incidence Using a Validated Administrative Data Algorithm. *Diabetes Care* 25, 512–516. doi:10.2337/diacare.25.3.512

Infanger, D., and Schmidt-Trucksäss, A. (2019). P Value Functions: An Underused Method to Present Research Results and to Promote Quantitative Reasoning. *Stat. Med.* 38, 4189–4197. doi:10.1002/sim.8293

Isbister, G. K., Brown, A. L., Gill, A., Scott, A. J., Calver, L., and Dunlop, A. J. (2017). QT Interval Prolongation in Opioid Agonist Treatment: Analysis of Continuous 12-Lead Electrocardiogram Recordings. *Br. J. Clin. Pharmacol.* 83, 2274–2282. doi:10.1111/bcp.13326

Kane, S. P. (2021). *The Top 200 of 2021, ClinCalc DrugStats Database, Version 21.1. ClinCalc.* Updated https://clincalc.com/DrugStats/Top200Drugs.aspx (Accessed December May 12, 2020 2021).

Kao, D., Bucher Bartelson, B., Khatri, V., Dart, R., Mehler, P. S., Katz, D., et al. (2013). Trends in Reporting Methadone-Associated Cardiac Arrhythmia, 1997-2011: an Analysis of Registry Data. *Ann. Intern. Med.* 158, 735–740. doi:10.7326/0003-4819-158-10-201305210-00008

Kao, D. P., Haigney, M. C., Mehler, P. S., and Krantz, M. J. (2015). Arrhythmia Associated with Buprenorphine and Methadone Reported to the Food and Drug Administration. *Addiction* 110, 1468–1475. doi:10.1111/add.13013

Kristensen, K., Christensen, C. B., and Christrup, L. L. (1995). The Mu1, Mu2, Delta, Kappa Opioid Receptor Binding Profiles of Methadone Stereoisomers and Morphine. *Life Sci.* 56, PL45–50. doi:10.1016/0024-3205(94)00426-s

Laber, E. B., and Shedden, K. (2017). Statistical Significance and the Dichotomization of Evidence: The Relevance of the ASA Statement on Statistical Significance and P-Values for Statisticians. *J. Am. Stat. Assoc.* 112, 902–904. doi:10.1080/01621459.2017.1311265

Qirjazi, E., McArthur, E., Nash, D. M., Dixon, S. N., Weir, M. A., Vasudev, A., et al. (2016). Risk of Ventricular Arrhythmia with Citalopram and Escitalopram: A Population-Based Study. *PLoS One* 11, e0160768. doi:10.1371/journal.pone.0160768

Rosen, D., Smith, M. L., and Reynolds, C. F., 3rd. (2008). The Prevalence of Mental and Physical Health Disorders Among Older Methadone Patients. *Am. J. Geriatr. Psychiatry* 16, 488–497. doi:10.1097/JGP.0b013e31816ff35a

Rothman, K. J., and Lash, T. L. (2021). "Precision and Study Size," in *Modern Epidemiology*. Editors T. L Lash, T. J. VanderWeele, S Haneuse, and K. J. Rothman. 4th ed. (Philadelphia: Wolters Kluwer), 263–286.

Roy, A. K., McCarthy, C., Kiernan, G., McGorrian, C., Keenan, E., Mahon, N. G., et al. (2012). Increased Incidence of QT Interval Prolongation in a Population Receiving Lower Doses of Methadone Maintenance Therapy. *Addiction* 107, 1132–1139. doi:10.1111/j.1360-0443.2011.03767.x

Saad, M. H., Savonen, C. L., Rumschlag, M., Todi, S. V., Schmidt, C. J., and Bannon, M. J. (2018). Opioid Deaths: Trends, Biomarkers, and Potential Drug Interactions Revealed by Decision Tree Analyses. *Front. Neurosci.* 12, 728. doi:10.3389/fnins.2018.00728

Schultz, S. E., Rothwell, D. M., Chen, Z., and Tu, K. (2013). Identifying Cases of Congestive Heart Failure from Administrative Data: a Validation Study Using Primary Care Patient Records. *Chronic Dis. Inj. Can.* 33, 160–166. doi:10.24095/hpcdp.33.3.06

Stringer, J., Welsh, C., and Tommasello, A. (2009). Methadone-Associated Q-T Interval Prolongation and Torsades De Pointes. *Am. J. Health Syst. Pharm.* 66, 825–833. doi:10.2146/ajhp070392

Tamariz, L., Harkins, T., and Nair, V. (2012). A Systematic Review of Validated Methods for Identifying Ventricular Arrhythmias Using Administrative and Claims Data. *Pharmacoepidemiol. Drug Saf.* 21 (1), 148–153. doi:10.1002/pds.2340

Tisdale, J. E., Jaynes, H. A., Kingery, J. R., Mourad, N. A., Trujillo, T. N., Overholser, B. R., et al. (2013). Development and Validation of a Risk Score to Predict QT Interval Prolongation in Hospitalized Patients. *Circ. Cardiovasc. Qual. Outcomes* 6, 479–487. doi:10.1161/CIRCOUTCOMES.113.000152

Titus-Lay, E. N., Jaynes, H. A., Tomaselli Muensterman, E., Walroth, T. A., Ott, C. A., Desta, Z., et al. (2021). Methadone-associated QT Interval Prolongation in Patients Undergoing Maintenance Therapy in an Urban Opioid Treatment Program. *Pharmacotherapy* 41, 238–246. doi:10.1002/phar.2498

Trinkley, K. E., Page, R. L., 2nd, Lien, H., Yamanouye, K., and Tisdale, J. E. (2013). QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr. Med. Res. Opin.* 29, 1719–1726. doi:10.1185/03007995.2013.840568

Tu, K., Campbell, N. R., Chen, Z. L., Cauch-Dudek, K. J., and McAlister, F. A. (2007). Accuracy of Administrative Databases in Identifying Patients with Hypertension. *Open Med.* 1, e18–26.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 26 April 2022
doi: 10.3389/fphar.2022.878972

Conventional Synthetic Disease-Modifying Anti-rheumatic Drugs for Psoriatic Arthritis: Findings and Implications From a Patient Centered Longitudinal Study in Brazil

Ronaldo José Faria[1,2], *Francisca Janiclecia Rezende Cordeiro*[2], *Jéssica Barreto Ribeiro dos Santos*[1,2], *Juliana Alvares-Teodoro*[3], *Augusto Afonso Guerra Júnior*[3], *Francisco de Assis Acurcio*[3] and *Michael Ruberson Ribeiro da Silva*[1,2]*

[1]Pharmaceutical Services Graduate Program, Federal University of Espírito Santo, Alegre, Brazil, [2]Health Assessment, Technology, and Economy Group, Federal University of Espírito Santo, Alegre, Brazil, [3]Department of Social Pharmacy, Federal University of Minas Gerais, Belo Horizonte, Brazil

Background: Conventional synthetic disease-modifying antirheumatic drugs are the first-line treatment to inhibit the progression of psoriatic arthritis. Despite their widespread clinical use, few studies have been conducted to compare these drugs for psoriatic arthritis.

Methods: a longitudinal study was carried out based on a centered patient national database in Brazil. Market share of drugs, medication persistence, drug costs, and cost per response were evaluated.

Results: a total of 1,999 individuals with psoriatic arthritis were included. Methotrexate was the most used drug (44.4%), followed by leflunomide (40.6%), ciclosporin (8.2%), and sulfasalazine (6.8%). Methotrexate and leflunomide had a greater market share than ciclosporin and sulfasalazine over years. Medication persistence was higher for leflunomide (58.9 and 28.2%), followed by methotrexate (51.6 and 25.4%) at six and 12 months, respectively. Leflunomide was deemed the most expensive drug, with an average annual cost of $317.25, followed by sulfasalazine ($106.47), ciclosporin ($97.64), and methotrexate ($40.23). Methotrexate was the drug being the lowest cost per response.

Conclusion: Methotrexate had the best cost per response ratio, owing to its lower cost and a slightly lower proportion of persistent patients when compared to leflunomide. Leflunomide had a slightly higher medication persistence than methotrexate, but it was the most expensive drug.

Keywords: psoriatic arthritis, pharmacoepidemiology, antirheumatic agents, medication adherence, drug costs

OPEN ACCESS

Edited by:
Mina Tadrous,
Women's College Hospital, Canada

Reviewed by:
Sawsan A. Zaitone,
Suez Canal University, Egypt
Douglas Veale,
University College Dublin, Ireland
Meghna Jani,
The University of Manchester, United Kingdom

***Correspondence:**
Michael Ruberson Ribeiro da Silva
michael.r.silva@ufes.br

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: *18 February 2022*
Accepted: *24 March 2022*
Published: *26 April 2022*

Citation:
Faria RJ, Cordeiro FJR, dos Santos JBR, Alvares-Teodoro J, Guerra Júnior AA, Acurcio FdA and da Silva MRR (2022) Conventional Synthetic Disease-Modifying Anti-rheumatic Drugs for Psoriatic Arthritis: Findings and Implications From a Patient Centered Longitudinal Study in Brazil. Front. Pharmacol. 13:878972. doi: 10.3389/fphar.2022.878972

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease with a wide range of symptoms. The four domains of musculoskeletal involvement in PsA are peripheral arthritis, dactylitis, enthesitis, and axial arthritis. Other non-musculoskeletal symptoms, such as uveitis, inflammatory bowel disease, nail psoriasis, and elevated acute phase reactants, help to diagnose PsA. Early diagnosis and treatment are difficult due to the non-specific and often subtle symptoms (Rida and Chandran, 2020).

The treatment of PsA has changed substantially over the past 10 years (Ogdie et al., 2020). Clinical practice guidelines have been created to assist clinicians in quickly integrating new therapeutic management knowledge into their practice. Treatment for PsA includes conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic therapies such as TNF inhibitors (TNFi), IL-17 inhibitors (IL-17i), IL-12/23 inhibitor (IL-12/23i), and new targeted oral agents including a phosphodiesterase-4 inhibitor and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) inhibitors (Coates and Helliwell, 2015; Gossec et al., 2015; Singh et al., 2018; Ogdie et al., 2020).

Synthetic drugs have been used to treat psoriatic arthritis since 1964. However, their use is largely derived from their utilization for rheumatoid arthritis (RA) and there is little evidence of clinical efficacy, usually restricted to peripheral outcomes for the short-term, without consistent long-term efficacy data (Coates and Helliwell, 2015). Methotrexate is known to be safe and effective in the treatment of RA and psoriasis, and it has been used to treat PsA despite scarce evidence from randomized controlled trials to support it. Some observational studies have supported the use of MTX, and current treatment recommendations approve its use as a first-line agent for the management of psoriatic arthritis with predominant peripheral arthritis (Elmanoum and Chandran, 2018; Coates et al., 2020). Furthermore, other csDMARD have also shown limited evidence of efficacy for the treatment of PsA (Kang and Kavanaugh, 2015).

Depending on the main impairment presented by the patient, the treatment takes different approaches. The EULAR and GRAPPA guidelines recommend starting with a csDMARD in most patients with treatment-naive predominantly peripheral arthritis. In addition, the GRAPPA guideline suggests that a biologic may be selected first if the situation warrants more aggressive therapy. Unless there are contraindications, EULAR recommends starting with methotrexate (MTX) as the first csDMARD. This recommendation was based on the efficacy of MTX in RA, similar medication persistence among patients with PsA and RA treated with MTX, data from the Tight Control in Psoriatic Arthritis trial, and expert opinion. The EULAR recommendations recognized the lack of data available at the time to support the use of MTX in clinical trials (Gossec et al., 2015; Coates et al., 2016; Singh et al., 2018; Ogdie et al., 2020).

In this sense, this study aimed to assess market share, medication persistence, drug costs, and cost per response in the treatment of PsA with csDMARD. Thus, a performance evaluation of the drugs available in Brazilian public health system was carried out to identify those with better performance and generate real world evidence for the treatment PsA.

METHODS

National Health Database

A National Health Database centered on the individual was created to conduct clinical, epidemiological, and economic studies using real-world evidence. This National Database incorporated health data from all 26 Brazilian states and the Federal District of individuals that used the Public National Health System. The data include records of inpatient care, outpatient care, and deaths from January 2000 to December 2015 (Guerra Junior et al., 2018). Psoriatic arthritis treatment was officially introduced in Brazil in 2010. As a result, the study's follow-up period lasted from 2010 to 2015. The data did not include information about the Brazilian private market, such as direct disbursements by individuals or health insurance coverage.

Patients and Market Share

Patients diagnosed with PsA according to Classification Criteria for Psoriatic Arthritis (CASPAR), with codes M07.0 and M07.3 from the International Classification of Diseases 10th version (ICD-10), who utilized cyclosporin, leflunomide, methotrexate, and sulfasalazine as first-line treatment in monotherapy were included. Patients using biological drugs concomitantly, with other osteoarticular inflammatory diseases or who had an absolute contraindication to the use of csDMARD were not eligible.

The first date of drug dispensation for the treatment of PsA was used to determine the date of entry into the follow-up. All patients were followed up on until their deaths or the end of the follow-up period.

Market share was assessed annually by identifying the number of patients being treated per drug in use in the public sector.

Medication Persistence

Medication persistence has been used as a proxy for effectiveness and safety of using antirheumatic agents (Luttropp et al., 2019; Ribeiro da Silva et al., 2019; Souza et al., 2021).

The absence of medication dispensation after 90 days from the last date of dispensation, a period corresponding to treatment renewal by SUS, was considered treatment discontinuation. The time between the first and last dispensation, plus a 30-days grace period (medication possession), was used to calculate the time until discontinuation. The proportion of people who remained on treatment was assessed after 6 and 12 months of follow-up for each drug. In addition, medication persistence in 18 and 24 months was presented.

Sensitivity analysis through propensity score weighting was used to control confounders at baseline and adjust the results to these. That is why inverse-probability weights were used to estimate the average treatment effect (ATE) on discontinuation time among drugs (Austin and Stuart, 2015).

Variables with statistically significant differences at baseline at a 5% significance level were included as balancing variables in the propensity score weighting.

Costs and Cost per Response

Cost analysis was developed from the perspective of the Brazilian Public Health System. The annual average direct costs with csDMARD were estimated using the macro-costing approach (top-down). The cost per response was calculated by dividing the costs by the response rate in 1 year of treatment.

The World Bank's conversion factor "purchasing power parity" (PPP) was used to adjust the monetary values. PPP rates are annual and provide a standard measurement by which countries' expenditure levels can be compared (World Bank, 2020).

The cost per response was calculated by dividing the annual drug cost by the observed medication persistence at 12-months follow-up period.

Statistical Analysis

Frequency distribution tables were elaborated for the categorical variables, and average with standard deviation (SD) or a confidence interval of 95% (CI95%) for the continuous variables. Kaplan-Meier curves were estimated to verify the time up to treatment discontinuation, that is, the loss of medication persistence. The log-rank test was used to verify if there were any differences among the groups for medication persistence.

Regression by the model of Cox proportional risks was used to verify the predictors of treatment discontinuation. Independent variables included in the model were age, sex, region of residence, csDMARD used, fragility index, and Charlson comorbidity index. A significance level of 20% was used for the bivariate analyses, and 5% was adopted for the multivariable analysis.

The Charlson comorbidity index, adapted from Quan et al. (2005), predicts mortality through the ponderation of patient comorbidities and it was used to measure the burden of the disease. The index score was calculated using data from outpatient and hospital medical services 3 years before entry into the cohort according 19 specified conditions. An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity (Quan et al., 2005). Days of hospitalizations for any cause were accounted for 2 years before the entry into the cohort, as a patient general frailty index (Neovius et al., 2013). The Charlson and frailty index were used as baseline indicators of general health in the study, which are related to occurrence comorbidities and hospitalizations, respectively.

Costs were compared through Analysis of Variance (ANOVA) with posthoc Bonferroni analysis. The analyses were developed using the software Stata® (Statistics/Data Analysis) version 16.1.

RESULTS

Sociodemographic and Clinical Characteristics of Patients

The study included 1,999 individuals with PsA on first-line treatment with csDMARD. The mean age of the patients was 51.11 years (12.77), with a predominance of females (60.1%). Most individuals resided in the Southeast and South regions, mainly in the states of São Paulo, Paraná, Rio Grande do Sul, Minas Gerais, and Santa Catarina. In contrast, the Northern region of the country represents only 0.8% of the study population. During follow-up, it was observed that 14.4% of the individuals experienced hospital admission. About 29% of patients had at least one out of 19 conditions specified by the Charlson Index (**Table 1**).

Methotrexate was the most used drug by patients (44.4% n = 887), followed by leflunomide (40.6%), ciclosporin (8.2%), and sulfasalazine (6.8%), as shown in **Table 1**.

Market Share of csDMARD

Methotrexate had a market share ranging from 41 to 48%, occasionally alternating the leading with leflunomide, which had a market share ranging from 34 to 46%. The market share of sulfasalazine and ciclosporin was lower than methotrexate and leflunomide. Sulfasalazine's market share has decreased over time, reaching 4% in 2015, whereas ciclosporin has maintained a market share of around 10% over time (**Figure 1**).

Medication Persistence

At 6-months follow-up, 53.4% of patients persisted in treatment with a mean time until to treatment discontinuation of 153.74 days (151.96–155.52). Patients treated with leflunomide presented highest medication persistence (58.9%; n = 478), followed by those treated with methotrexate (51.6%; n = 458). Patients taking sulfasalazine (44.8% n = 61) and ciclosporin (42.7%; n = 70) had a lower medication persistence ($p < 0.001$).

At the end of the first year of follow-up, patients using leflunomide remained with the slightly higher medication persistence (28.2% n = 229) than patients using methotrexate (25.4% = 458). Similar to the 6-month follow-up analysis, patients who used ciclosporin and sulfasalazine for 12 months maintained a lower medication persistence. Patients using leflunomide presented higher medication persistence than ones using other csDMARD ($p < 0.05$) (**Table 2**).

In addition, patients taking leflunomide were more persistent in treatment at 18 (18.5%) and 24 (12.2%) months. Methotrexate comes next with 13.1% (18 months) and 8.8% (24 months) of medication persistence. Moreover, patients treated with sulfasalazine and ciclosporin had a higher discontinuation rate, with only 8.8% (18 months) and 8.1% (24 months) of the patients initially treated with sulfasalazine and 7.9% (18 months) and 4.3% (24 months) of those treated with ciclosporin persisting with therapy (log-rank < 0,05) (**Figure 2**).

Sensitivity analysis confirmed the original findings, with patients taking leflunomide maintaining higher medication persistence than patients taking the other drugs after covariates balance at baseline (**Table 3**).

At 12-months of follow-up, approximately 66% of non-persistent patients discontinued the treatment, while 34% switched or added a new medication to the treatment. Sulfasalazine and cyclosporine had a higher proportion of treatment discontinuations than leflunomide and methotrexate. Among the patients who switched or added drugs

TABLE 1 | Baseline characteristics of PsA patients who used csDMARD.

Variables	csDMARD (n = 1.999)	Ciclosporin (n = 164)	Leflunomide (n = 812)	Methotrexate (n = 887)	Sulfasalazine (n = 136)	*p*-value	Obs
Female n (%)	1202 (60.1)	75 (45.7)	533 (65.6)	515 (58.1)	79 (58.1)	<0.001	a
Male n (%)	797 (39.9)	89 (54.3)	279 (34.4)	372 (41.9)	57 (41.9)		
Age in years mean (SD)	51.11 (12.77)	46.68 (13.68)	52.05 (12.22)	51.26 (12.73)	49.89 (14.03)	<0.001	b
Region or residence n (%)	—	—	—	—	—	<0.001	c
Southeast	1022 (51.1)	95 (57.9)	431 (53.1)	421 (47.5)	75 (55.1)	—	—
South	754 (37.7)	35 (21.3)	286 (35.2)	394 (44.4)	39 (28.7)	—	—
Northeast	138 (6.9)	18 (11.0)	59 (7.3)	51 (5.7)	10 (7.4)	—	—
Central west	69 (3.4)	15 (9.1)	29 (3.6)	19 (2.1)	6 (4.4)	—	—
North	16 (0.8)	1 (0.6)	7 (0.9)	2 (0.2)	6 (4.4)	—	—
State of residence n (%)	—	—	—	—	—	<0.001	c
São Paulo	686 (34.2)	75 (45.7)	248 (30.5)	298 (33.6)	65 (47.8)	—	—
Paraná	256 (12.8)	20 (12.2)	44 (5.4)	178 (20.1)	14 (10.3)	—	—
Rio Grande do Sul	299 (15.0)	2 (1.2)	156 (19.2)	126 (14.2)	15 (11.0)	—	—
Minas Gerais	195 (9.8)	4 (2.4)	103 (12.7)	83 (9.4)	5 (3.7)	—	—
Santa Catarina	199 (10.0)	13 (7.9)	86 (10.6)	90 (10.1)	10 (7.4)	—	—
Outros	364 (18.2)	50 (30.6)	175 (21.6)	112 (12.6)	27 (19.8)	—	—
Frailty index n (%)	288 (14.4)	22 (13.4)	93 (11.5)	155 (17.5)	18 (13.2)	0.567	d
Frailty index mean (SD)	1.36 (5.77)	1.47 (5.68)	1.24 (6.42)	1.53 (5.41)	0.87 (3.76)	0.324	d
Charlson index n (%)	576 (28.8)	40 (24.4)	267 (32.9)	220 (25.8)	49 (36.0)	<0.001	e
Charlson index mean (*SD*)	0.40 (0.87)	0.38 (0.93)	0.43 (0.80)	0.36 (0.82)	0.60 (1.36)	0.094	f
Gini index mean (*SD*)	0.52 (0.07)	0.538 (0.077)	0.519 (0.071)	0.511 (0.071)	0.515 (0.070)	<0.001	g

CsDMARD, conventional synthetic DMARD., Obs, observation.

[a]*significant for all comparisons, except for methotrexate versus sulfasalazine.*

[b]*significant only for ciclosporin versus methotrexate and ciclosporin versus leflunomide.*

[c]*significant for all comparisons.*

[d]*no significance for all comparisons.*

[e]*significant for all comparisons, except for methotrexate versus ciclosporin and ciclosporin versus sulfasalazine.*

[f]*significant only for sulfasalazine versus methotrexate and sulfasalazine versus ciclosporin.*

[g]*significant for all comparisons, except for sulfasalazine versus methotrexate and sulfasalazine versus leflunomide.*

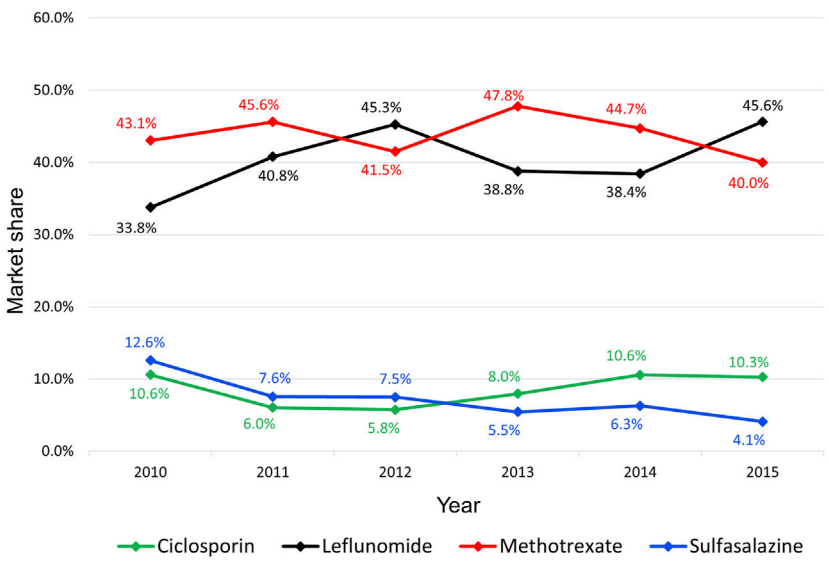


FIGURE 1 | Market share of csDMARD for psoriatic arthritis from 2010 to 2015.

TABLE 2 | Medication persistence at 6 and 12 months of follow-up.

Drug	Medication Persistence n (%)	Time until Discontinuation Mean (CI 95%)	Medication Persistence n (%)	Time until Discontinuation Mean (CI 95%)
	6 months		12 months	
Leflunomide (n = 812)	478 (58.9)	159.89 (157.41–162.38)	229 (28.2)	237.68 (230.36–245.00)
Methotrexate (n = 887)	458 (51.6)	150.90 (148.03–153.76)	225 (25.4)	219.06 (211.67–226.45)
Sulfasalazine (n = 136)	61 (44.8)	144.09 (136.83–151.14)	32 (19.5)	199.34 (183.24–215.45)
Ciclosporin (n = 164)	70 (42.7)	146.61 (140.49–152.73)	24 (17.6)	195.84 (177.97–213.71)
Total (n = 1.999)	1,067 (53.4)	153.74 (151.96–155.52)	510 (25.5)	223.43 (218.62–228.23)
p-value	<0.001[a]	<0.001[b]	0.014[c]	<0.001[b]

[a]*significant for leflunomide versus methotrexate, leflunomide versus sulfasalazine, leflunomide versus ciclosporin, and methotrexate versus ciclosporin. No differences for other comparisons.*
[b]*significant for leflunomide versus methotrexate, leflunomide versus sulfasalazine, and leflunomide versus ciclosporin. No differences for other comparisons.*
[c]*significant for leflunomide versus sulfasalazine and leflunomide versus ciclosporin. No differences for other comparisons.*

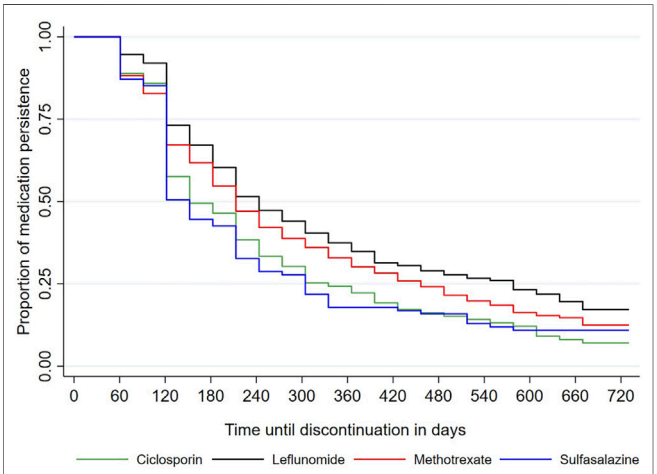


FIGURE 2 | Medication persistence of csDMARD for psoriatic arthritis.

to the treatment, most started using biological drugs, especially adalimumab (**Table 4**).

Predictors of Non-persistence in the Use of csDMARD

The predictors of non-persistence to treatment were younger patients, living in the northern and northeastern regions of the country, and who were not on leflunomide. Thus, it was possible to identify that the risk of treatment discontinuation decreases with increasing age (Hazard ratio [HR] = 0.995, 95% confidence interval [95% CI] 0.991–0.991). The risk of treatment discontinuation of the northeastern and northern regions was 75% higher than south, southeast, and central-west of Brazil (HR = 1.750, 95% CI 1,471–2,084). Finally, patients using methotrexate, sulfasalazine, and ciclosporin also have a higher risk of discontinuing treatment. Patients taking sulfasalazine had a hazard risk of 1.39 for discontinuation (39% higher), followed by ciclosporin with 1.30 (30% higher), and methotrexate with 1.16 (16% higher) compared to leflunomide (**Table 5**). Socioeconomic inequality (measured by GINI), comorbidity index, and frailty index were not identified as predictors of treatment discontinuation.

Drug Costs and Cost per Response

The mean annual cost per patient was $105.32 (171.34) at 12 months of follow-up, and a statistically significant difference was observed in the spending among drugs ($p < 0.001$), except for ciclosporin versus sulfasalazine. Leflunomide was considered the drug with the highest cost, with an average of $317.25, followed by sulfasalazine ($106.47), ciclosporin ($97.64), being methotrexate the lowest cost drug ($40.23) (**Table 6**).

Despite being the drug with the best medication persistence, leflunomide was the drug with the highest cost. In this sense, leflunomide had the highest cost per responding patient. Methotrexate, on the other hand, had the lowest drug cost and the lowest cost per responder being considered the most efficient drug.

TABLE 3 | Average treatment effect after propensity score weighting: pairwise analyses.

Pairwise Comparison	6 months				12 months		
	ATE	CI 95%	*p*-value		ATE	CI 95%	*p*-value
MTX vs. LEF	−9.91	−13.68; −6.13	<0.001	MTX vs. LEF	−21.76	−32.01; −11.51	<0.001
CCP vs. LEF	−10.70	−11.21; −4.65	0.001	CCP vs. LEF	−36.85	−55.61; −18.09	<0.001
SSZ vs. LEF	−15.53	−22.90; −8.16	<0.001	SSZ vs. LEF	−40.99	−60.81; −21.17	<0.001
CCP vs. MTX	−1.25	−7.89; 5.39	0.712	CCP vs. MTX	−14.71	−31.21; 3.79	0.119
SSZ vs. MTX	−5.91	−13.45; 1.62	0.124	SSZ vs. MTX	−19.53	−39.32; 0.26	0.053
SSZ vs. CCP	−3.89	−13.24; 5.45	0.414	SSZ vs. CCP	−4.48	−29.65; 20.69	0.727

CCP: ciclosporin; LEF: leflunomide; MTX: methotrexate; SSZ: sulfasalazine. ATE: average treatment effect.

TABLE 4 | Withdrawal and switch treatments at 12 months.

Ciclosporin n (%)		Leflunomide n (%)		Methotrexate n (%)		Sulfasalazine n (%)	
Withdraw	Switch	Withdraw	Switch	Withdraw	Switch	Withdraw	Switch
90 (68.2)	42 (31.8)	348 (59.7)	235 (40.3)	406 (61.3)	256 (38.7)	74 (66.1)	38 (33.9)
Switch - 42 (100)		**Switch - 235 (100)**		**Switch - 256 (100)**		**Switch - 38 (100)**	
22 (55.4) = ADA		**100 (42.5) = ADA**		**91 (35.5) = ADA**		**10 (26.3) = ADA**	
9 (21.4) = ETA		**62 (26.4) = ETA**		69 (27.0) = LEF		9 (23.7) = MTX	
56 (14.3) = LEF		53 (22.6) = MTX		**48 (18.8) = ETA**		9 (23.7) = LEF	
3 (7.4) = IFX		**16 (6.8) = IFX**		**26 (10.2) = IFX**		**8 (21.1) = ETA**	
2 (7.4) = MTX or SSZ		12 (5.1) CCP or SSZ		12 (4.7) = SSZ		**3 (7.9) = IFX**	

ADA: adalimumab; CCP: ciclosporin; ETA: etanercept; IFX: infliximab; LEF: leflunomide; MTX: methotrexate; SSZ: sulfasalazine. Bold: biologic DMARD.

TABLE 5 | Predictors of treatment discontinuation at 12 months of follow-up.

Variables	Crude HR (CI 95%)	*p*-value	Adjusted HR (CI 95%)	*p*-value
Sex				
Female	1	—	—	—
Male	0.965 (0.869–1.170)	0.500	—	—
Age	0.994 (0.990–0.998)	0.002	0.995 (0.991–0.999)	0.010
Region				
South/Southeast/Central west	1	—	1	—
Northeast/North	1.779 (1.495–2.116)	<0.001	1.750 (1.471–2.084)	<0.001
CsDMARD				
Leflunomide	1	—	1	—
Methotrexate	1.150 (1.029–1.744)	0.014	1.160 (1.038–1.297)	0.009
Sulfasalazine	1.424 (1.163–1.744)	0.001	1.387 (1.133–1.699)	0.002
Ciclosporin	1.371 (1.135–1.657)	0.001	1.297 (1.071–1.570)	0.008
GINI	3.522 (1.707–7.271)	0.001	—	—
Charlson Index	1.055 (1.002–1.110)	0.040	—	—
Frailty Index	1.006 (0.998–1.119)	0.119	—	—

HR, hazard ratio; CI95% = Confidence interval 95%; csDMARD, conventional synthetic DMARD.

TABLE 6 | Drug costs and cost per response of csDMARD.

csDMARD	Annual cost		Response Rate	Cost per Response		Rank
	BRL	PPP dolar		BRL	PPP dolar	
Total	404.87 (358.85)	171.34 (151.86)	0.255	1,587.73	671.92	—
Methotrexate	95.06 (105.71)	40.23 (44.74)	0.254	374.25	158.39	1
Leflunomide	749.67 (228.42)	317.25 (96.96)	0.282	2,658.40	1,125.00	4
Sulfasalazine	251.58 (137.47)	106.47 (58.17)	0.176	1,429.43	604.94	3
Ciclosporin	230.73 (107.09)	97.64 (45.32)	0.195	1,183.23	500.72	2
p-value	<0.001[a]	<0.001[a]	—	—	—	—

BRL: brazilian real; PPP: purchasing power parity.

[a]*< 0.001 for all comparisons, except for ciclosporin versus sulfasalazine.*

DISCUSSION

This is the first national study in Brazil comparing multiple csDMARDs for psoriatic arthritis. These are significant findings, indicating that methotrexate has the best cost-benefit ratio, while leflunomide has the best treatment persistence but the highest cost of all drugs assessed.

Some studies have observed the performances of csDMARDs in the treatment of psoriatic arthritis (Farr et al., 1988; Gupta, 1989; Farr et al., 1990; Combe et al., 1996; Fraser, 2005; Malesci et al., 2007; Ricci et al., 2011; Behrens et al., 2013; Nikiphorou et al., 2014; Landi et al., 2018; Ribeiro da Silva et al., 2019; Jacobs et al., 2020; Maksabedian Hernandez et al., 2020), among which five allow the comparison of drugs (Malesci et al., 2007; Landi et al., 2018; Ribeiro da Silva et al., 2019; Jacobs et al., 2020; Maksabedian Hernandez et al., 2020), with increasing the relevance of these findings. In addition, one clinical trial has been conducted to assess methotrexate for PsA (Mulder et al., 2020). As a result, the findings are important to better understand the reality of treatment with these drugs in a real-world setting. It was observed that the patients had a mean age of 51.11 years, with the highest proportion (31.4%) in the group with an age range between 46 and 55 years, which corroborates data from the literature showing that the peak incidence of PsA occurs between the fourth and fifth decades of life (Liu, 2014). In a multicenter study in Italy involving 37 rheumatology centers, the mean age found was 49 years (Cervini et al., 2011). In the United States, an epidemiological study identified that disease onset occurs on average at 46.4 years (Karmacharya et al., 2021).

Considering that the use of conventional synthetic disease course modifying drugs are the first line of treatment for psoriatic arthritis, one can infer that the average age of diagnosis of psoriatic arthritis in Brazil is around 50 years old. When compared to data from the United States, which indicate an onset of the disease at 46.4 years of age, possible difficulty in diagnosing the disease in Brazil can be investigated. Clinical guidelines indicate that delay in diagnosis is a major challenge that needs to be addressed, as it negatively impacts treatment outcomes. Thus, strategies to promote early referral and decrease the delay in diagnosis and treatment of inflammatory arthritis are needed (Gossec et al., 2015; Haroon et al., 2015).

This is a problem that has been faced in Brazil and one of the challenges encountered is represented by the concentration of rheumatology physicians in large cities and the low availability of rheumatologists in the public health system (da Silva et al., 2019a; da Silva et al., 2019b).

The present study showed a slight predominance of females (60.1%), which is common in other studies conducted in Brazil. However, in studies with large databases, a similar distribution of the disease between genders is usually observed (da Silva et al., 2019b).

Among the drugs evaluated in the cohort, methotrexate was the most used among patients, followed by leflunomide, ciclosporin, and sulfasalazine. This finding corroborates the clinical protocols for the treatment of PsA, where methotrexate is recommended as the first choice for the treatment of the disease. Methotrexate is recommended for the treatment of peripheral joint and skin involvement in PsA, preferably at a dose greater than 15 mg per week subcutaneously, due to the adverse events seen with the oral route. If methotrexate is not available, ciclosporin, leflunomide or sulfasalazine should be used in patients with peripheral arthritis (Coates and Helliwell, 2015; Gossec et al., 2015; Singh et al., 2018; Carneiro et al., 2021).

According to Kane and collaborators, methotrexate was the most prescribed csDMARD in an American hospital. Despite clinical improvement with csDMARD use, 47% of patients had radiological damage at a median interval of 2 years (Kane, 2003). Leflunomide has been evaluated in a few observational studies and has shown benefits in improving peripheral and skin outcomes, with concomitant use with methotrexate leading to a greater likelihood of achieving a 50% improvement in the Psoriasis Area Surface Index (PASI50). Additionally, benefits were observed in the control of pain, fatigue, and dactylitis (Behrens et al., 2013).

Methotrexate is one of the most widely used cDMARDs worldwide for the treatment of PsA, although few clinical trials have evaluated its efficacy, and clinical evidence is still limited (Fraser, 2005; Coates and Helliwell, 2015).

Old clinical trials, with small sample size, indicated that the use of sulfasalazine in the treatment of PsA is safe but had a limited efficacy (Combe et al., 1996; Farr et al., 1990; Farr et al., 1988). Limited clinical evidence is available for ciclosporin in the treatment of PsA, which indicates possible benefits from its use (Gupta, 1989). In combination with methotrexate, ciclosporin appears to control inflammation but not pain and quality of life for patients (Fraser, 2005).

Medication persistence at 6 months was 58.9% for leflunomide, 51.6% for methotrexate, 44.8% for sulfasalazine, and 42.7% for ciclosporin. There was a significant decrease in medication persistence after 120 days of the start of therapy, which was due to the first renewal of treatment in the SUS occurring during this time (treatment renewal occurs every 3 months). Following discontinuation, part of the patients switched the therapy, mainly to a biological drug (da Silva et al., 2019a; da Silva et al., 2019b). At 12 months, medication persistence reduced to 28.2% for leflunomide, 25.2% for methotrexate, 19.5% for ciclosporin, and 17.6% for sulfasalazine. Therefore, differences in medication persistence were minimal for leflunomide and methotrexate.

There are no clinical trials that directly compare csDMARD for the treatment of PsA (Kang and Kavanaugh, 2015). Additionally, few observational studies have evaluated more than one csDMARD for PsA, with medication persistence the most common outcome reported (Ribeiro da Silva et al., 2019; Jacobs et al., 2020). In a retrospective cohort study with 187 adult PsA patients in the Netherlands, patients using first-line methotrexate presented higher medication persistence than ones using sulfasalazine (log-rank < 0.05). At 1 year of treatment, patients on methotrexate had a retention rate of approximately 70%, while patients on sulfasalazine had 50%. The main reasons for csDMARD retention failure in PsA are treatment inefficacy (52%) and side effects (28%) (Jacobs et al., 2020).

In an Argentine cohort study, 87 adult PsA patients completed the follow-up. According to the findings, methotrexate was the most commonly used csDMARD, followed by leflunomide.

Methotrexate had a higher cumulative survival rate than leflunomide and was aided by concomitant steroid therapy, whereas leflunomide had a higher survival rate in elderly patients (Landi et al., 2018).

In a retrospective study with 63 patients using methotrexate and leflunomide in Brazil, no difference was observed in the medication persistence. At 12 months, 37.7% of patients on leflunomide and 34.0% on methotrexate remained on treatment (Ribeiro da Silva et al., 2019).

Overall, medication persistence with csDMARDs is lower than biological drugs in Brazil (da Silva et al., 2019b) and other countries (Murage et al., 2018; Murray et al., 2021). According to Murage and collaborators, medication persistence for TNF inhibitors can vary from 50 to 75% at 12 months, depending on biologic drug in use (Murage et al., 2018). Murray and collaborators found an overall medication persistence of 59% at 12 months for biological therapy in psoriatic arthritis (Murray et al., 2021).

In this sense, there is a rapid shift from synthetic to biological therapy, and the reasons for this must be investigated, owing primarily to the failure of synthetic treatment and the higher cost of biological therapies (da Silva et al., 2019b; Maksabedian Hernandez et al., 2020). Thus, observational studies in Brazil and other countries evaluating the effectiveness and safety of these drugs for psoriatic arthritis could be recommended.

In this study, patients who were treated with leflunomide and methotrexate were the most persistent, while individuals taking ciclosporin and sulfasalazine showed a higher rate of discontinuation in the treatment of PsA. Methotrexate and leflunomide are usually the csDMARD investigated in observational studies for PsA, and the results are comparable between them (Landi et al., 2018; Ribeiro da Silva et al., 2019). Sulfasalazine appeared only in one study versus methotrexate, with a worse result of persistence (Jacobs et al., 2020).

Methotrexate had a medication persistence of 51.6% at 6 months and 25.4% for 12 months. These findings differ from a study conducted in Italy that found 80 and 69% persistence for 6 and 12 months, respectively (Ricci et al., 2011). Another American study brings similar results to those found in this research, where 34.1 and 25.2% of patients remained in treatment with methotrexate and sulfasalazine respectively after 1 year of follow-up (Maksabedian Hernandez et al., 2020).

In summary, differences in medication persistence have been observed when comparing studies (Landi et al., 2018; Ribeiro da Silva et al., 2019; Jacobs et al., 2020). This can be explained by differences concerning organization and access to health services, arising from regional inequities and methodological differences between studies.

This is corroborated by the lower medication persistence observed in patients living in the North and Northeast regions of the country, since these regions have worse social and economic indicators, in contrast to the South and Southeast regions, with better economic and social indicators. In Brazil, access to health services is strongly influenced by the supply of supplementary health services, people's social status, and where they live (Kang and Kavanaugh, 2015). On the other hand, access improvements have already been observed in the North and Northeast regions in recent years (Cambota and Rocha, 2015; Albuquerque et al., 2017).

Younger individuals had a higher discontinuation rate. This finding is similar to an Argentine cohort, which found that patients older than 50 years treated with leflunomide had a higher persistence to treatment (Landi et al., 2018). This effect was also observed for methotrexate, but the patients treated with this drug were on steroids (Ribeiro da Silva et al., 2019).

In terms of drug costs, leflunomide showed the highest cost, followed by sulfasalazine, ciclosporin, and methotrexate. Methotrexate was the drug being the lowest cost per response. Despite leflunomide demonstrating superior medication persistence, its higher cost is a disadvantage when compared to other csDMARD. In this regard, lowering the cost of leflunomide may improve its efficiency for PsA (Gupta, 1989). In addition, drug costs for csDMARDs are very less than biological drugs (Gupta, 1989; Ricci et al., 2011).

This study has advantages and limitations. As for advantages, it is noteworthy that this is the first study with a large sample size to evaluate csDMARD for the treatment of psoriatic arthritis. This is of particular importance given the scarcity of studies evaluating these drugs. Additionally, the use of Unified Health System databases can contribute to the generation of useful knowledge to reassess and support decision-making in health. In this sense, it appears that Brazil has a large amount of data that has been organized to carry out pharmacoepidemiological studies (Guerra Junior et al., 2018; Leal et al., 2022).

As for disadvantages, we mention the impossibility of identifying the causes of treatment discontinuation, such as ineffectiveness, side effects, among others. In addition, it was not possible to stratify patients using oral and subcutaneous methotrexate. Furthermore, this database lacks clinical data on disease activity, which was one of the study's limitations. At last, the data were paired with the identification of the patient's line of care until 2015, which precluded analysis of a more recent period.

CONCLUSION

The current study adds to the understanding above the use of csDMARDS for the treatment of PsA. Methotrexate and leflunomide were the most used csDMARDs. Methotrexate had the best cost per response ratio, owing to its lower cost and a slightly lower proportion of persistent patients when compared to leflunomide. Leflunomide had the highest medication persistence, but it was also the most expensive

drug. The rate of treatment discontinuation was relatively high for all drugs. As a result, it is recognized that there is a need for the development of actions aimed at improving outcomes related to psoriatic arthritis treatment to contribute to better pharmacotherapy for these patients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

RJF and FJRC contribute to the data analysis, interpretation of data, drafting of the work. JBRS contributes to the conception and design of the work and revising it critically. JA-T, AAGJ, and FAA contribute to the conception of the work, data acquisition, and revising critically the work. MRRS contributes to the design of the work, data acquisition, data analysis, interpretation of data, and drafting the work. All authors approved the final version and agreed to be accountable for all aspects of the work.

REFERENCES

Albuquerque, M. V. d., Viana, A. L. d. Á., Lima, L. D. d., Ferreira, M. P., FusaroER e Iozzi, E. R., and Iozzi, F. L. (2017). Desigualdades regionais na saúde: mudanças observadas no Brasil de 2000 a 2016. *Ciênc. Saúde Coletiva* 22 (4), 1055–1064. doi:10.1590/1413-81232017224.26862016

Austin, P. C., and Stuart, E. A. (2015). Moving towards Best Practice when Using Inverse Probability of Treatment Weighting (IPTW) Using the Propensity Score to Estimate Causal Treatment Effects in Observational Studies. *Stat. Med.* 34 (28), 3661–3679. doi:10.1002/sim.6607

Behrens, F., Finkenwirth, C., Pavelka, K., Štolfa, J., Šipek-Dolnicar, A., Thaçi, D., et al. (2013). Leflunomide in Psoriatic Arthritis: Results from a Large European Prospective Observational Study. *Arthritis Care Res. (Hoboken)* 65 (3), 464–470. doi:10.1002/acr.21848

Cambota, J. N., and Rocha, F. F. (2015). Determinantes das desigualdades na utilização de serviços de saúde: análise para o Brasil e regiões. *Pesq Planej Econ.* 45 (2), 219–243.

Carneiro, S., Palominos, P. E., Anti, S. M. A., Assad, R. L., Gonçalves, R. S. G., Chiereghin, A., et al. (2021). Brazilian Society of Rheumatology 2020 Guidelines for Psoriatic Arthritis. *Adv. Rheumatol.* 61 (1), 69. doi:10.1186/s42358-021-00219-y

Cervini, C., Leardini, G., Mathieu, A., Punzi, L., and Scarpa, R. (2011). Psoriatic Arthritis: Epidemiological and Clinical Aspects in a Cohort of 1.306 Italian Patients. *Reumatismo* 57 (4), 283–290. doi:10.4081/reumatismo.2005.283

Coates, L. C., and Helliwell, P. S. (2015). Methotrexate Efficacy in the Tight Control in Psoriatic Arthritis Study. *J. Rheumatol.* 43 (2), 356–361. doi:10.3899/jrheum.150614

Coates, L. C., Merola, J. F., Grieb, S. M., Mease, P. J., and Callis Duffin, K. (2020). Methotrexate in Psoriasis and Psoriatic Arthritis. *J. Rheumatol. Suppl.* 96, 31–35. doi:10.3899/jrheum.200124

Coates, L. C., Kavanaugh, A., Mease, P. J., Soriano, E. R., Laura Acosta-Felquer, M., Armstrong, A. W., et al. (2016). Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheumatol.* 68 (5), a–n. doi:10.1002/art.39573

Combe, B., Goupille, P., Kuntz, J. L., Tebib, J., Lioté, F., and Bregeon, C. (1996). Sulphasalazine in Psoriatic Arthritis: a Randomized, Multicentre, Placebo-Controlled Study. *Br. J. Rheumatol.* 35 (7), 664–668. doi:10.1093/rheumatology/35.7.664

da Silva, M. R. R., dos Santos, J. B. R., Almeida, A. M., Alvares-Teodoro, J., Kakehasi, A. M., and Acurcio, F. A. (2019a). Access to High-Cost Medications for Psoriatic Arthritis in the National Health System in Brazil: the Long Path up to Dispensation. *Adv. Rheumatol.* 59 (1), 48. doi:10.1186/s42358-019-0091-7

da Silva, M. R. R., dos Santos, J. B. R., Almeida, A. M., Guerra Júnior, A. A., Alvares Teodoro, J., and Acurcio, F. A. (2019b). Biological Therapy in the Treatment of Psoriatic Arthritis: Economic and Epidemiological Considerations. *Expert Rev. Clin. Immunol.* 15 (8), 879–887. doi:10.1080/1744666X.2019.1631798

Elmamoun, M., and Chandran, V. (2018). Role of Methotrexate in the Management of Psoriatic Arthritis. *Drugs* 78 (6), 611–619. doi:10.1007/s40265-018-0898-2

Farr, M., Kitas, G. D., Waterhouse, L., Jubb, R., Felix-Davies, D., and Bacon, P. A. (1990). Sulphasalazine in Psoriatic Arthritis: a Double-Blind Placebo-Controlled Study. *Br. J. Rheumatol.* 29 (1), 46–49. doi:10.1093/rheumatology/29.1.46

Farr, M., Kitas, G. D., Waterhouse, L., Jubb, R., Felix-Davies, D., and Bacon, P. A. (1988). Treatment of Psoriatic Arthritis with Sulphasalazine: a One Year Open Study. *Clin. Rheumatol.* 7 (3), 372–377. doi:10.1007/BF02239195

Fraser, A. D., van Kuijk, A. W., Westhovens, R., Karim, Z., Wakefield, R., Gerards, A. H., et al. (2005). A Randomised, Double Blind, Placebo Controlled, Multicentre Trial of Combination Therapy with Methotrexate Plus Ciclosporin in Patients with Active Psoriatic Arthritis. *Ann. Rheum. Dis.* 64 (6), 859–864. doi:10.1136/ard.2004.024463

Gossec, L., Smolen, J. S., Ramiro, S., de Wit, M., Cutolo, M., Dougados, M., et al. (2015). European League against Rheumatism (EULAR) Recommendations for the Management of Psoriatic Arthritis with Pharmacological Therapies: 2015 Update. *Ann. Rheum. Dis.* 75 (3), 499–510. doi:10.1136/annrheumdis-2015-208337

Guerra Junior, A. A., Pereira, R. G., Gurgel, E. I., Cherchiglia, M., Dias, L. V., Ávila, J. D., et al. (2018). Building the National Database of Health Centred on the Individual: Administrative and Epidemiological Record Linkage - Brazil, 2000-2015. *Int. J. Popul. Data Sci.* 3 (1), 446. doi:10.23889/ijpds.v3i1.446

Gupta, A. K., Matteson, E. L., Ellis, C. N., Ho, V. C., Tellner, D. C., Voorhees, J. J., et al. (1989). Cyclosporine in the Treatment of Psoriatic Arthritis. *Arch. Dermatol.* 125 (4), 507–510. doi:10.1001/archderm.125.4.507

Haroon, M., Gallagher, P., and FitzGerald, O. (2015). Diagnostic Delay of More Than 6 Months Contributes to Poor Radiographic and Functional Outcome in Psoriatic Arthritis. *Ann. Rheum. Dis.* 74 (6), 1045–1050. doi:10.1136/annrheumdis-2013-204858

Jacobs, M. E., Pouw, J. N., Welsing, P., Radstake, T. R. D. J., and Leijten, E. F. A. (2020). First-line csDMARD Monotherapy Drug Retention in Psoriatic Arthritis: Methotrexate Outperforms Sulfasalazine. *Rheumatology (Oxford)* 60 (2), 780–784. doi:10.1093/rheumatology/keaa399

Kane, D., Stafford, L., Bresnihan, B., and FitzGerald, O. (2003). A Prospective, Clinical and Radiological Study of Early Psoriatic Arthritis: an Early Synovitis Clinic Experience. *Rheumatology (Oxford)* 42 (12), 1460–1468. doi:10.1093/rheumatology/keg384

Kang, E. J., and Kavanaugh, A. (2015). Psoriatic Arthritis: Latest Treatments and Their Place in Therapy. *Ther. Adv. Chronic Dis.* 6 (4), 194–203. doi:10.1177/2040622315582354

Karmacharya, P., Crowson, C. S., Bekele, D., Achenbach, S. J., Davis, J. M., Ogdie, A., et al. (2021). The Epidemiology of Psoriatic Arthritis over Five Decades: A Population-Based Study. *Arthritis Rheumatol.* 73 (10), 1878–1885. doi:10.1002/art.41741

Leal, L. F., Osorio-de-Castro, C. G. S., de Souza, L. J. C., de Ferre, F., Ferre, D. M., Ito, M., et al. (2021). Data Sources for Drug Utilization Research in Brazil-DUR-BRA Study. *Front. Pharmacol.* 12, 789872. doi:10.3389/fphar.2021.789872

Liu, J. T., Yeh, H. M., Liu, S. Y., and Chen, K. T. (2014). Psoriatic Arthritis: Epidemiology, Diagnosis, and Treatment. *World J. Orthop.* 5 (4), 537–543. doi:10.5312/wjo.v5.i4.537

Luttropp, K., Dozier, M., Justo, N., Cornillie, F., Kachroo, S., Govoni, M., et al. (2019). Real-world Treatment Persistence of Golimumab in the Management of Immune-Mediated Rheumatic Diseases in Europe: a Systematic Literature Review. *BMJ Open* 9 (5), e027456. doi:10.1136/bmjopen-2018-027456

M, L., Ca, Z., O, C., Yanzi J, G., Ee, S., I, C., et al. (2018). Methotrexate and Leflunomide Survival in Patients with Psoriatic Arthritis. *Int. J. Clin. Rheumatol.* 13 (2), 881–884. doi:10.4172/1758-4272.1000170

Maksabedian Hernandez, E. J., Tkacz, J., Lopez-Gonzalez, L., Higgins, K., Ogdie, A., and Stolshek, B. S. (2020). Psoriatic Arthritis Treatment Patterns and Costs Among Pharmacologic Treatment-Naïve Patients. *Am. J. Manag. Care* 26 (8), e252–e257. doi:10.37765/ajmc.2020.44075

Malesci, D., Tirri, R., Buono, R., and La Montagna, G. (2007). Leflunomide in Psoriatic Arthritis: a Retrospective Study of Discontinuation Rate in Daily Clinical Practice Compared with Methotrexate. *Clin. Exp. Rheumatol.* 25, 881–884.

Mulder, M. L. M., Vriezekolk, J. E., den Broeder, N., Mahler, E. A. M., Helliwell, P. S., van den Hoogen, F. H. J., et al. (2020). Comparing Methotrexate Monotherapy with Methotrexate Plus Leflunomide Combination Therapy in Psoriatic Arthritis: Protocol of a Randomized, Placebo-Controlled, Double-Blind Clinical Trial (COMPLETE-PsA). *Trials* 21 (1), 155. doi:10.1186/s13063-020-4097-6

Murage, M. J., Tongbram, V., Feldman, S. R., Malatestinic, W. N., Larmore, C. J., Muram, T. M., et al. (2018). Medication Adherence and Persistence in Patients with Rheumatoid Arthritis, Psoriasis, and Psoriatic Arthritis: a Systematic Literature Review. *Patient Prefer Adherence* 12, 1483–1503. doi:10.2147/PPA.S167508

Murray, K., Turk, M., Alammari, Y., Young, F., Gallagher, P., Saber, T., et al. (2021). Long-term Remission and Biologic Persistence Rates: 12-year Real-World Data. *Arthritis Res. Ther.* 23 (1), 25. doi:10.1186/s13075-020-02380-z

Neovius, M., Arkema, E. V., Olsson, H., Eriksson, J. K., Kristensen, L. E., Simard, J. F., et al. (2013). Drug Survival on TNF Inhibitors in Patients with Rheumatoid Arthritis Comparison of Adalimumab, Etanercept and Infliximab. *Ann. Rheum. Dis.* 74 (2), 354–360. doi:10.1136/annrheumdis-2013-204128

Nikiphorou, E., Negoescu, A., Fitzpatrick, J. D., Goudie, C. T., Badcock, A., Östör, A. J., et al. (2014). Indispensable or Intolerable? Methotrexate in Patients with Rheumatoid and Psoriatic Arthritis: a Retrospective Review of Discontinuation Rates from a Large UK Cohort. *Clin. Rheumatol.* 33 (5), 609–614. doi:10.1007/s10067-014-2546-x

Ogdie, A., Coates, L. C., and Gladman, D. D. (2020). Treatment Guidelines in Psoriatic Arthritis. *Rheumatology (Oxford)* 59 (Suppl. ment_1), i37–i46. doi:10.1093/rheumatology/kez383

Quan, H., Sundararajan, V., Halfon, P., Fong, A., Burnand, B., Luthi, J. C., et al. (2005). Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data. *Med. Care* 43 (11), 1130–1139. doi:10.1097/01.mlr.0000182534.19832.83

Ribeiro da Silva, M. R., Ribeiro dos Santos, J. B., Maciel Almeida, A., Itria, A., Maria Kakehasi, A., Alvares Teodoro, J., et al. (2019). Medication Persistence for Psoriatic Arthritis in a Brazilian Real-World Setting. *Future Sci. OA* 5 (2), FSO369. doi:10.4155/fsoa-2018-0101

Ricci, M., De Marco, G., Desiati, F., Mazzocchi, D., Rotunno, L., Battafarano, N., et al. (2011). Long-term Survival of Methotrexate in Psoriatic Arthritis. *Reumatismo* 61 (2), 125–131. doi:10.4081/reumatismo.2009.125

Rida, M. A., and Chandran, V. (2020). Challenges in the Clinical Diagnosis of Psoriatic Arthritis. *Clin. Immunol.* 214, 108390. doi:10.1016/j.clim.2020.108390

Singh, J. A., Guyatt, G., Ogdie, A., Gladman, D. D., Deal, C., Deodhar, A., et al. (2018). American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheumatol.* 71 (1), 5–32. doi:10.1002/art.40726

Souza, A. F., Da Silva, M. R., Dos Santos, J. B., Almeida, A. M., Acurcio, F. A., and Alvares-Teodoro, J. (2021). Medication Adherence and Persistence of Psoriatic Arthritis Patients Treated with Biological Therapy in a Specialty Pharmacy in Brazil: a Prospective Observational Study. *Pharm. Pract. (Granada)* 19 (2), 2312. doi:10.18549/pharmpract.2021.2.2312

World Bank (2020). International Comparison Program Database. Available at: https://data.worldbank.org/indicator/PA.NUS.PPP?end=2020&locations=BR&start=2010.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 27 April 2022
doi: 10.3389/fphar.2022.886652

Psychotropic Medication Use Before and During COVID-19: A Population-Wide Study

Christine Leong[1,2]*, *Kaarina Kowalec*[1,3], *Sherif Eltonsy*[1], *James M. Bolton*[2,4,5], *Murray W. Enns*[2], *Qier Tan*[6], *Marina Yogendran*[6], *Dan Chateau*[7], *Joseph A. Delaney*[1,8], *Jitender Sareen*[2,4,5], *Jamison Falk*[1], *Rae Spiwak*[9], *Sarvesh Logsetty*[2,9] and *Silvia Alessi-Severini*[1]

[1]College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [2]Department of Psychiatry, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden, [4]Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [5]Department of Psychology, University of Manitoba, Winnipeg, MB, Canada, [6]Manitoba Centre for Health Policy, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [7]Research School of Population Health, College of Health and Medicine, Australian National University, Canberra, ACT, Australia, [8]Department of Epidemiology, University of Washington, Seattle, WA, United States, [9]Department of Surgery, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

OPEN ACCESS

Edited by:
Andrea Burden,
ETH Zürich, Switzerland

Reviewed by:
Ben Beaglehole,
University of Otago, Christchurch, New Zealand
Janet Sultana,
Mater Dei Hospital, Malta

***Correspondence:**
Christine Leong
Christine.leong@umanitoba.ca

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: 28 February 2022
Accepted: 23 March 2022
Published: 27 April 2022

Citation:
Leong C, Kowalec K, Eltonsy S, Bolton JM, Enns MW, Tan Q, Yogendran M, Chateau D, Delaney JA, Sareen J, Falk J, Spiwak R, Logsetty S and Alessi-Severini S (2022) Psychotropic Medication Use Before and During COVID-19: A Population-Wide Study. Front. Pharmacol. 13:886652. doi: 10.3389/fphar.2022.886652

Background: The coronavirus disease 2019 (COVID-19) pandemic and public health measures that took place have led to concerns regarding mental health and receipt of psychotropic medications. We aimed to study the changes in psychotropic medication dispensation rates before and during the COVID-19 pandemic in the general population.

Methods: Administrative health data from the Canadian province of Manitoba was used to describe the quarterly incidence and prevalence of antipsychotics, antidepressants, and anxiolytic/sedative-hypnotics from January 1, 2015 to December 31, 2020. Individuals who received at least one prescription within each quarter were considered exposed to the medication. The denominator was the total population within each quarter. Incidence was defined as no receipt of medication in the 3 years prior to the quarter of interest. Autoregression models for time series data plus indicator variables were used to compare each quarter of 2020 after public health measures were implemented in March 2020 in relation to the expected trend. Analyses were stratified by age and sex.

Results: There were 1,394,885 individuals in the first quarter of 2020, with a mean (SD) age of 38.9 (23.4) years, 50.3% were female, and 36.1% had a psychiatric diagnosis in the previous 5 years. A significant decrease was observed for incident antidepressant use ($p < 0.05$ for both sexes and all age groups except for those 65 years and older) and anxiolytic use ($p < 0.05$ for both sexes and all age groups except 80 years and older) in the second quarter (April-June) of 2020 compared to the expected trend. Females and those aged 40 years and older had a significantly higher incidence of antidepressant and antipsychotic use in the final quarter of 2020 compared to the expected trend ($p < 0.05$).

Conclusion: Our findings indicate a decrease in new prescriptions for antidepressants and anxiolytics in the 3 months after COVID-19 in-person restrictions were first

implemented. We then observed an increase in the new use of antidepressants and antipsychotics at the end of 2020, in females and people aged 40 years and older, with the highest rates of use in the population 80 years and older.

Keywords: psychotropic drugs, COVID-19, pandemic, drug utilization, population-wide study

INTRODUCTION

The mental health and wellbeing of individuals during the coronavirus disease 2019 (COVID-19) pandemic and after public health measures took place has been at the forefront of concerns related to the pandemic (Canadian Centre on Substance Use and Addiction, 2020; Holmes et al., 2020; Gunnell et al., 2020; Vigo et al., 2020; Canadian Mental Health Association National Survey, 2020). National surveys in Canada reported increased anxiety, depression, and substance use (Canadian Mental Health Association National Survey, 2020; Mental Health Commission of Canada and Canadian Centre, 2021; Vindegaard and Benros, 2020), with 40% of Canadians reporting a decline in mental health since March 2020 (Mental Health Commission of Canada and Canadian Centre, 2021). Changes in financial circumstances, social isolation, and the health of family members were identified as the top three stressors related to the pandemic (Vindegaard and Benros, 2020; Mental Health Commission of Canada and Canadian Centre, 2021). Internationally, the rate of insomnia and symptoms of depression and anxiety increased during the initial months of the pandemic compared to the previous year (Li et al., 2020; Voitsidis et al., 2020; Kokou-Kpolou et al., 2020; The COVID-19 Healthcare Coalition Telehealth Impact Study Work Group, 2020). Understanding the mental health effects of COVID-19 and related public health measures has become an important research priority (Gunnell et al., 2020; Holmes et al., 2020). Examining trends of psychotropic medication prescribing provides important information on pandemic-related distress and health service use.

During the pandemic, the public has experienced restrictions to in-person healthcare visits (**Supplementary Appendix SI**), and these measures have shifted the way in which people were able to seek care. A higher rate of virtual visits in place of in-person for outpatient mental health care has been observed during the pandemic (Grekou et al., 2021). It is anticipated that such changes would have an impact on the prescribing of certain psychotropic medications, such as antidepressants, antipsychotics, and anxiolytic/sedative-hypnotics. Furthermore, it is uncertain whether there will be differences in the incidence and prevalence of psychotropic medication by age and sex. Previous reports have noted that females experienced greater challenges during the pandemic as a result of unemployment and unreliable childcare (Centre for Addiction and Mental Health, 2020; Thibaut and van Wijngaarden-Cremers, 2020; Statsitics Canada, 2021). In contrast, the mental health of older adults was found to be less affected by the pandemic compared to the younger population (Roos et al., 2005; Vahia et al., 2020). A shift in psychotropic medication prescribing can have implications on the health outcomes of patients. Identifying groups with greater incidence or prevalence of psychotropic medication is essential for gaining a better understanding of drug prescribing and need for targeted interventions to address potential mental health impacts of the pandemic.

Administrative data can provide rich information on the real-world effects of a pandemic on medication use. The objective of this study was to determine if the quarterly incidence and prevalence of psychotropic medication use changed from 2015 to 2020 in the general population and whether this differed by age and sex. At the time the study was conducted, we hypothesized that psychotropic medication incidence and prevalence would decrease in the second quarter of 2020 after the new restrictions to in-person visits took place followed by an increase in psychotropic use in the last quarter of 2020. We also hypothesized that females and younger adults will have higher incidence and prevalence in psychotropic medication use compared to males and other age groups, respectively, during the pandemic.

MATERIALS AND METHODS

Data Source

This was a longitudinal whole population observational study using administrative health data from the Manitoba Population Research Data Repository located at the Manitoba Centre for Health Policy (MCHP). This repository, which has been used extensively for population-wide research (Roos and Nicol, 1999; Daumit et al., 2003), contains data on physician visits, hospitalizations, and medication dispensing that is, not restricted to age, income, or healthcare coverage, for all residents of Manitoba (a population of approximately 1.4 million). A significant strength of these data is that the Drug Program Information Network (DPIN) contains information on the strength, days supply, quantity, and date of prescription filled for all Manitoba residents regardless of age or drug coverage, except for medications received in the hospital and nursing stations. Physician claims data and hospital discharge abstracts provided information on contacts with the healthcare system and diagnoses using the International Classification of Diseases, Clinical Modification (ICD-9-CM or ICD-10-CA equivalent) codes. The Manitoba Health Insurance Registry provided demographic information on age, sex, and urban/rural residence at the beginning of each interval. Statistics Canada census files provided income quintile information. This study was approved by the Human Research Ethics Board of the University of Manitoba and the Manitoba Health Seniors and Active Living (MHSAL) Health Information Privacy Committee (HIPC). These factors give us the unique capacity to study populations often under-represented in administrative-based studies conducted in other jurisdictions.

Population

All community-dwelling individuals not restricted by age living in Manitoba with at least 1 day of MHSAL coverage between

January 1, 2015 and December 31, 2020 were included. For each quarter or year of interest, the denominator for the general population was the sum of individuals who were listed in the MHSAL registry for at least 1 day of coverage during that quarter or year. Manitoba residents who were dispensed ≥1 psychotropic or non-psychotropic medication within each quarter from January 1, 2015 to December 31, 2020 were identified as the population of psychotropic or non-psychotropic medication users, respectively. Data from 2015 to 2019 was included to allow us to account for underlying trends in utilization in the period prior to the pandemic. Those with a mental disorder during the study period were further described by the following categories: mood and/or anxiety, psychosis, schizophrenia, personality disorder, and substance use disorder using ICD codes previously used in research conducted at MCHP (See **Supplementary Appendix SII** for ICD codes) (Daumit et al., 2003; Brownell et al., 2012; Smith et al., 2013; Brownell et al., 2015; Chartier et al., 2015).

Drug Exposure

All medications included in the analysis were identified using their Anatomic Therapeutic Classification (ATC) code (World Health Organization, 2021). Psychotropic medications included antidepressants (ATC N06A and N06CA), anxiolytic/sedative-hypnotics (including benzodiazepines and z-drug hypnotics, N05B, N05C, and N03AE01), and antipsychotic agents (N05A, except N05AN). Medication exposure was defined as at least one dispensation of the medication of interest within each calendar quarter (quarter 1 was January-March, quarter 2 was April-June, quarter 3 was July-September, and quarter 4 was October-December).

Statistical Analyses

Demographic characteristics including age (≤18, 19–39, 40–64, 65–79, ≥80 years old), sex, region of residence, socioeconomic status [(SES) based on neighborhood income quintile] and psychiatric disorder type in the previous 5 years (mood/anxiety, psychosis, substance use disorder, personality disorder, schizophrenia) (MCHP Concept Dictionary, 2016) for the first quarter of 2020 were described using summary statistics.

The primary analysis described the quarterly prevalence and incidence rates of dispensed psychotropic medications from January 1, 2015 to December 31, 2020 overall and then stratified by age group and sex. Incident users were defined as those who had not been dispensed a medication from the drug class of interest in the 3 years prior to their first dispensation. The rate of dispensing of each drug class was determined for each quarter by counting the number of individuals dispensed a prescription for that medication class divided by the total number of individuals in that quarter for the general population and expressed as per 1,000 people in the general population per quarter.

Autoregression models for time series data plus indicator variables were used to examine rates of psychotropic medication use before and after the second quarter of 2020 using interrupted time series models with autocorrelation to look at quarterly incidence and prevalence. Of note, because the data show a unique fluctuation in quarterly rates after the time after public health restrictions took place in March, an indicator variable was used to determine if the quarterly rates of Q2, Q3, and Q4 of 2020 were significantly different from the secular trends in the model. A coefficient expressing the difference from expected from each of the three quarters of 2020 was reported. Statistical significance was set at $p < 0.05$. SAS statistical software (version 9.4, SAS Institute, Cary, NC) was used for all analyses.

TABLE 1 | Demographics of the study population for the first quarter of 2020 (N = 1,394,885).

Demographic	Frequency (%)
Mean age (years)	38.9 (SD 23.4)
Age group (years)	
≤18	330,398 (23.7)
19–39	403,129 (28.9)
40–64	435,354 (31.2)
65–79	167,991 (12.0)
≥80	58,013 (4.2)
Female sex	701,368 (50.3)
Income quintile (1 = lowest; 5 = highest)	
Rural 1	107,078 (7.7)
Rural 2	107,838 (7.7)
Rural 3	108,083 (7.8)
Rural 4	107,114 (7.7)
Rural 5	105,369 (7.6)
Urban 1	169,395 (12.1)
Urban 2	168,661 (12.1)
Urban 3	169,218 (12.1)
Urban 4	169,994 (12.2)
Urban 5	170,216 (12.2)
Not found	11,919 (0.85)
Urban residence (Winnipeg/Brandon)	858,118 (61.5)
Psychiatric diagnosis in last 5 years	503,575 (36.1)
Mood/Anxiety	404,822 (29.0)
Psychosis	59,522 (4.3)
Substance use disorder	50,658 (3.6)
Personality disorder	9,025 (0.7)
Schizophrenia	8,806 (0.6)

RESULTS

The study population in the first quarter of each year ranged from 1,331,188 in 2015 to 1,394,885 in 2020. The demographic characteristics of the study population at the beginning of the first quarter of 2020 are shown in **Table 1**. The mean (SD) age was 38.9 (23.4) years, 50.3% were female, and 61.5% resided in an urban residence. There were 36.1% who were diagnosed with a mental disorder in the previous 5 years, with 29% having a history of mood or anxiety disorder.

Antidepressants

Overall, the incidence of antidepressant dispensations ranged from 5.6 per 1,000 in quarter 1 of 2015 to 6.9 per 1,000 in the final quarter of 2020, while the prevalence of antidepressant use increased from 79.9 per 1,000 in the first quarter of 2015 to 108.6 per 1,000 in the final quarter of 2020 (**Supplementary Appendix SIV**). The incidence of antidepressant use was lowest in the second quarter

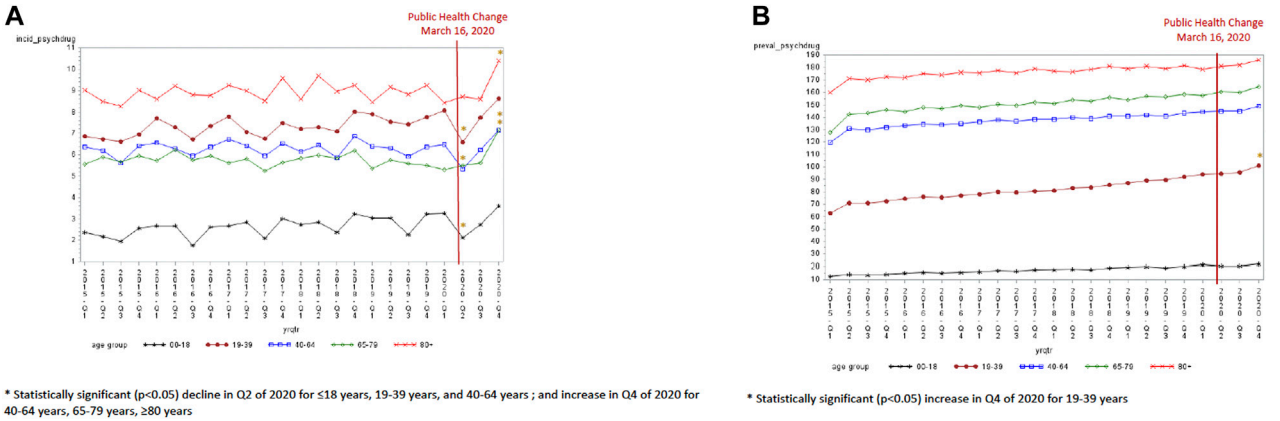


FIGURE 1 | (A) Antidepressant incidence by age group (per 1,000). **(B)** Antidepressant prevalence by age group (per 1,000).

TABLE 2 | Coefficient estimate (standard error, SE) and *p*-value measuring the difference in incidence rates from the expected trend in each quarter of 2020 after public health restrictions were implemented.

Parameter	Q2 (Apr-June 2020)	3 (Jul-September 2020)	Q4 (Oct-December 2020)
Antidepressant			
≤18 years	−0.97 (0.38, p = 0.02)*	−0.41 (0.39, p = 0.30)	0.42 (0.39, p = 0.29)
19–39 years	−1.27 (0.38, p = 0.003)*	−0.15 (0.38, p = 0.70)	0.67 (0.39, p = 0.10)
40–64 years	−1.04 (0.34, p = 0.006)*	−0.16 (0.34, p = 0.64)	0.77 (0.35, p = 0.04)*
65–79 years	−0.091 (0.28, p = 0.75)	0.044 (0.28, p = 0.88)	1.59 (0.29, p < 0.0001)*
≥80 years	−0.31 (0.42, p = 0.47)	−0.43 (0.43, p = 0.32)	1.33 (0.44, p = 0.007)*
Female	−1.14 (0.35, p = 0.004)*	−0.097 (0.36, p = 0.79)	1.25 (0.36, p = 0.003)*
Male	−0.76 (0.26, p = 0.009)*	−0.32 (0.27, p = 0.25)	0.29 (0.27, p = 0.29)
Anxiolytic/Sedative-Hypnotic			
≤18 years	−0.41 (0.11, p = 0.002)*	0.11 (0.12, p = 0.35)	−0.23 (0.12, p = 0.06)
19–39 years	−1.01 (0.25, p = 0.0006)*	−0.35 (0.25, p = 0.18)	−0.93 (0.25, p = 0.002)*
40–64 years	−1.10 (0.34, p = 0.005)*	−0.72 (0.35, p = 0.05)	−1.11 (0.35, p = 0.005)*
65–79 years	−0.85 (0.30, p = 0.01)*	−0.53 (0.31, p = 0.10)	−0.74 (0.31, p = 0.03)*
≥80 years	−0.11 (0.53, p = 0.85)	−0.08 (0.54, p = 0.89)	−0.061 (0.54, p = 0.91)
Female	−1.04 (0.19, p < 0.0001)*	−0.35 (0.19, p = 0.08)	−0.93 (0.19, p = 0.0001)*
Male	−0.64 (0.23, p = 0.01)*	−0.38 (0.23, p = 0.12)	−0.60 (0.23, p = 0.019)*
Antipsychotic			
≤18 years	−0.045 (0.11, p = 0.68)	−0.075 (0.11, p = 0.50)	0.17 (0.11, p = 0.15)
19–39 years	−0.20 (0.12, p = 0.12)	−0.0064 (0.13, p = 0.96)	0.13 (0.13, p = 0.31)
40–64 years	−0.16 (0.11, p = 0.16)	−0.088 (0.11, p = 0.43)	0.29 (0.11, p = 0.02)*
65–79 years	0.18 (0.17, p = 0.31)	0.25 (0.18, p = 0.17)	0.82 (0.18, p = 0.0002)*
≥80 years	0.10 (0.37, p = 0.01)*	0.71 (0.37, p = 0.07)*	1.88 (0.38, p < 0.0001)*
Female	−0.05 (0.12, p = 0.64)	0.06 (0.12, p = 0.60)	0.52 (0.12, p = 0.0004)*
Male	−0.06 (0.11, p = 0.56)	−0.03 (0.11, p = 0.77)	0.17 (0.11, p = 0.13)

of 2020 (5.09 per 1,000) and the highest in the last quarter of 2020 (6.87 per 1,000). The groups aged ≤18 years [−0.97, standard error (SE) 0.38, p = 0.02], 19–39 years (−1.27, SE 0.38, p = 0.0031), and 40–64 years (−1.04, SE 0.34, p = 0.006) experienced a statistically significant decline in incident antidepressant use in the second quarter of 2020 compared to the expected trend (**Figure 1A** and **Table 2**). A statistically significant increase in the incidence of antidepressant use was seen in the last quarter of 2020 for those 40 years and older (40–64 years old: 0.77, SE 0.34, p = 0.04; 65–79 years old: 1.59, SE 0.29, p < 0.0001; and ≥80 years old: 1.33, SE 0.44, p = 0.007). An increase in the prevalence of antidepressant use was observed in the last quarter of 2020 relative to the expected trend for the population aged 19–39 years (4.77, SE 1.80, p = 0.016) only (**Figure 1B** and **Table 3**).

Both males and females experienced a decline in antidepressant incidence in the second quarter of 2020 (4.09 per 1,000 for males and 6.08 per 1,000 for females) (**Figure 2A**). This decline in quarter 2 was significantly lower than the expected trend for both males (−0.76, SE 0.26, p = 0.009) and females (−1.14, SE 0.35, p = 0.004). However, females experienced a greater increase in antidepressant incidence than males in the last quarter of 2020 (8.52 per 1,000 in quarter 4 of 2020 for females and 5.19 per 1,000 in quarter 4 of 2020 for males). This increase in quarter 4 was significantly higher than the expected trend for

TABLE 3 | Coefficient estimate (standard error, SE) and *p*-value measuring the difference in prevalence rates from the expected trend in each quarter of 2020 after public health restrictions were implemented.

Parameter	Q2 (Apr-June 2020)	Q3 (Jul-September 2020)	Q4 (Oct-December 2020)
Antidepressant			
≤18 years	−0.66 (0.53, p = 0.23)	−1.03 (0.53, p = 0.07)	0.28 (0.54, p = 0.61)
19–39 years	0.80 (1.76, p = 0.65)	0.66 (1.78, p = 0.72)	4.77 (1.80, p = 0.02)*
40–64 years	−0.87 (2.51, p = 0.73)	−1.70 (2.54, p = 0.51)	1.66 (2.57, p = 0.53)
65–79 years	−0.17 (3.47, p = 0.96)	−1.84 (3.52, p = 0.61)	1.64 (3.56, p = 0.65)
≥80 years	−2.25 (2.91, p = 0.45)	−1.85 (2.94, p = 0.54)	1.54 (2.98, p = 0.61)
Female	−0.17 (2.37, p = 0.94)	−0.21 (2.40, p = 0.93)	4.07 (2.43, p = 0.11)
Male	−0.66 (1.10, p = 0.56)	−1.03 (1.12, p = 0.37)	0.80 (1.13, p = 0.49)
Anxiolytic/Sedative-Hypnotic			
≤18 years	−0.66 (0.23, p = 0.009)*	0.21 (0.23, p = 0.38)	−0.28 (0.23, p = 0.25)
19–39 years	−2.04 (1.31, p = 0.13)	−1.73 (1.32, p = 0.21)	−2.33 (1.34, p = 0.098)
40–64 years	−3.47 (2.75, p = 0.22)	−5.44 (2.78, p = 0.065)	−5.20 (2.82, p = 0.08)
65–79 years	−3.26 (4.72, p = 0.50)	−6.17 (4.78, p = 0.21)	−5.88 (4.84, p = 0.24)
≥80 years	−0.94 (4.45, p = 0.84)	−4.75 (4.51, p = 0.31)	−0.93 (4.57, p = 0.84)
Female	−2.57 (2.27, p = 0.27)	−3.40 (2.29, p = 0.15)	−3.46 (2.32, p = 0.15)
Male	−1.86 (1.36, p = 0.21)	−2.20 (1.37, p = 0.13)	−2.22 (1.39, p = 0.13)
Antipsychotic			
≤18 years	0.30 (0.17, p = 0.10)	0.18 (0.17, p = 0.31)	0.51 (0.18, p = 0.01)*
19–39 years	0.33 (0.29, p = 0.26)	0.50 (0.29, p = 0.10)	1.18 (0.30, p = 0.0008)*
40–64 years	0.27 (0.25, p = 0.28)	0.15 (0.25, p = 0.56)	0.62 (0.25, p = 0.02)*
65–79 years	0.28 (0.34, p = 0.42)	0.85 (0.35, p = 0.02)*	1.43 (0.35, p = 0.0006)*
≥80 years	1.96 (0.98, p = 0.06)	2.70 (0.99, p = 0.01)*	3.70 (1.00, p = 0.002)*
Female	0.50 (0.28, p = 0.09)	0.81 (0.28, p = 0.01)	1.47 (0.29, p < 0.0001)*
Male	0.22 (0.24, p = 0.36)	0.16 (0.24, p = 0.51)	0.52 (0.25, p = 0.046)*

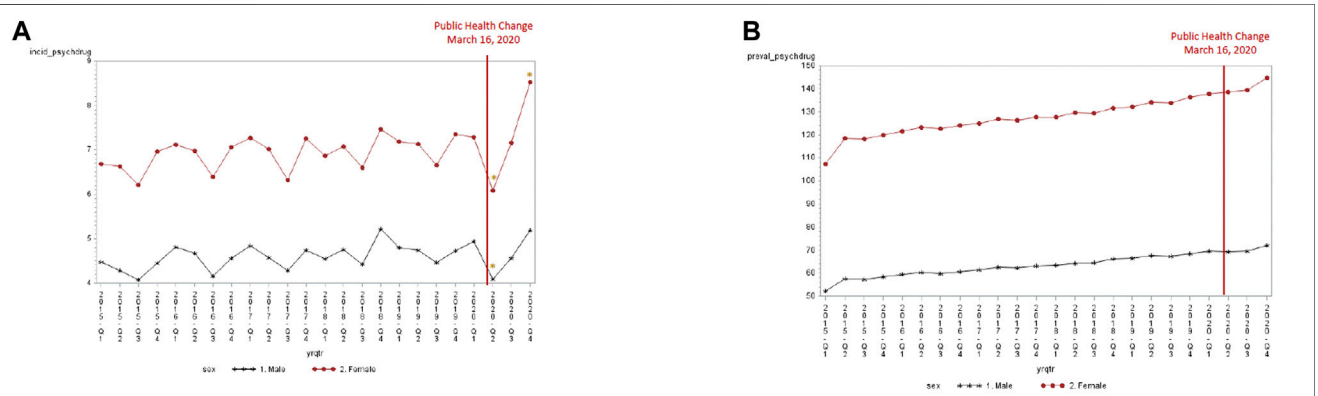


FIGURE 2 | (A) Antidepressant incidence by sex (per 1,000). **(B)** Antidepressant prevalence by sex (per 1,000).

females (1.25, SE 0.36, p = 0.003) but not for men (0.29, SE 0.27, p = 0.29). The prevalence of antidepressant use was higher for females and males in the last quarter of 2020 (144.7 per 1,000 for females versus 72.1 per 1,000 for males). However, the increase in prevalence in the final quarter of 2020 was not significantly different than the expected trend (4.07, SE 2.4, p = 0.111 for females and 0.80, SE 1.13, p = 0.50 for men) (**Table 3**).

Anxiolytic/Sedative-Hypnotics

Overall, the incidence (6.2 per 1,000 in Q1 of 2015 to 3.9 per 1,000 in Q4 of 2020) and prevalence (63.5 per 1,000 in Q1 of 2015 to 56.3 per 1,000 in Q4 of 2020) use of anxiolytic/sedative-hypnotics declined from 2015 to 2019 (**Supplementary Appendix SIV**). All age groups experienced a decline in anxiolytic/sedative-hypnotic incidence in quarter 2 of 2020 (**Figure 3A**). The decline in quarter 2 was significant for all age groups except for those 80 years and older (−0.06, SE 0.54, p = 0.912) when compared to the expected trend. The incidence of anxiolytic/sedative-hypnotics were also significantly lower than the expected trend in the final quarter of 2020 for those aged 19–39 years (−0.93, SE 0.25, p = 0.002), 40–64 years (−1.11, SE 0.35, p = 0.005), and 65–79 years (−0.74, SE 0.31, p = 0.027). Only the population aged <18 years

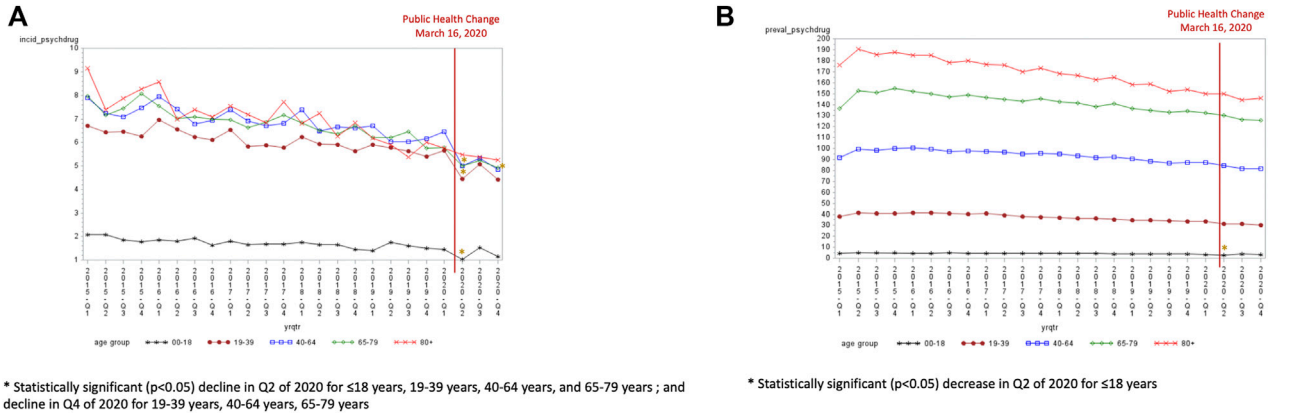


FIGURE 3 | (A) Anxiolytic/sedative-hypnotic incidence by age group (per 1,000). **(B)** Anxiolytic/sedative-hypnotic prevalence by age group (per 1,000).

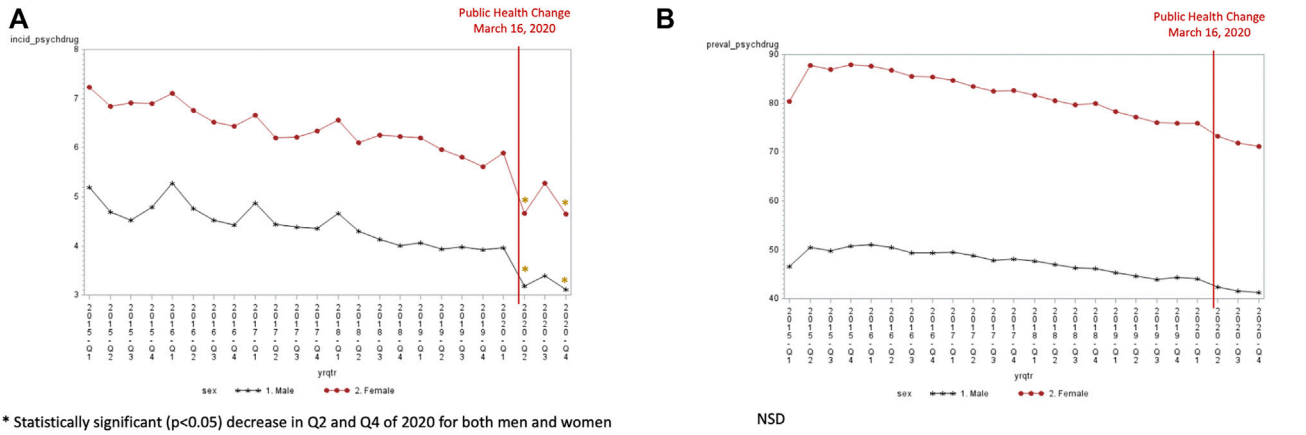


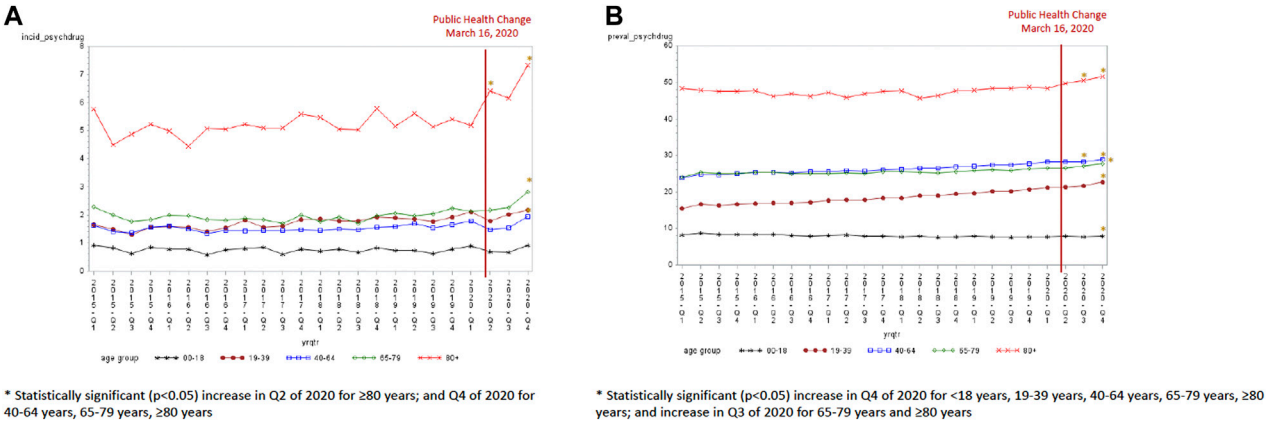
FIGURE 4 | (A) Anxiolytic/sedative-hypnotic incidence by sex (per 1,000). **(B)** Anxiolytic/sedative-hypnotic prevalence by sex (per 1,000).

experienced a significant decline in prevalence in Q2 of 2020 compared to the expected trend (−0.66, SE 0.23, p = 0.009) (**Figure 3B**).

Both males and females experienced a decline in anxiolytic/sedative-hypnotic incidence in the second quarter of 2020 (3.18 per 1,000 for men and 4.66 per 1,000 for females) (**Figure 4A**). This decline in quarter 2 of 2020 was significantly lower than the expected trend for both males (−0.64, SE 0.23, p = 0.011) and females (−1.04, SE 0.19, p < 0.0001). The decline was also significantly lower in quarter 4 of 2020 than the expected trend for both males (−0.60, SE 0.23, p = 0.019) and females (−0.93, SE 0.19, p = 0.0001). The prevalence of anxiolytic/sedative-hypnotics were not significantly different in quarters 2 to 4 of 2020 compared to the expected trend for both males and females (**Figure 4B**).

Antipsychotics

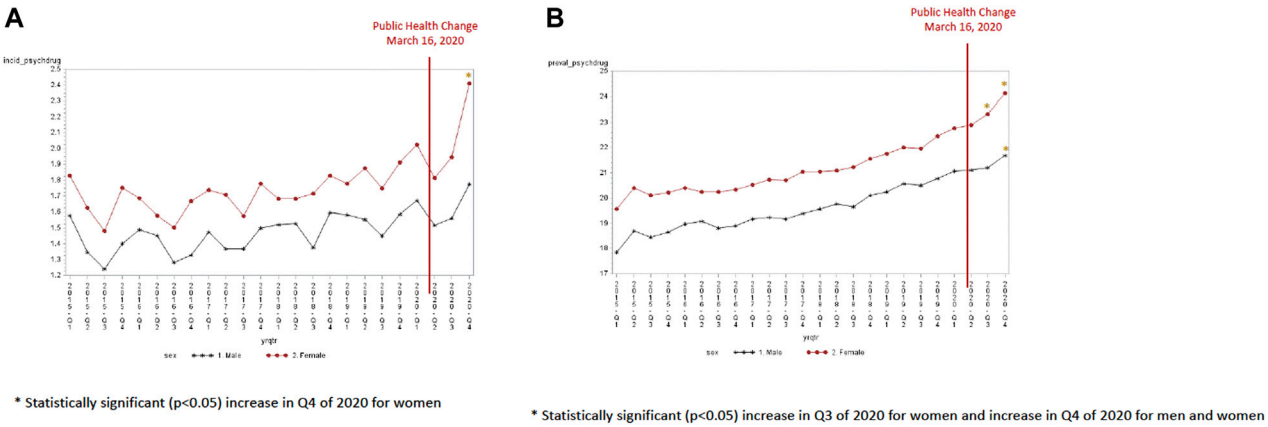
Overall, an increase in the incidence (1.70/1,000 in Q1:2015 to 1.85/1,000 in Q1:2020) and in the prevalence (18.71/1,000 in Q1:2015 to 21.92/1,000 in Q1:2020) of antipsychotic use was observed from 2015 to 2020 (**Supplementary Appendix SIV**). The incidence of antipsychotics was highest in the Q4:2020 (2.09/1,000) and the incidence was significantly higher in Q4 of 2020 than the expected trend for those 40 years and older (40 years old: 0.29, SE 0.11, p = 0.02; 65–79 years: 0.82, SE 0.18, p = 0.0002; ≥80 years old: 1.87, SE 0.38, p < 0.0001) (**Figure 5A**). Antipsychotic incident use was the highest in the 80+ years of age population at 7.33 per 1,000 in the fourth quarter of 2020. The prevalence of antipsychotic use significantly increased for all age groups in quarter 4 of 2020 compared to the expected trend (**Figure 5B**). A significant increase in antipsychotic prevalence was also observed in quarter 3 of 2020 for those 65–79 years (1.43, SE 0.35, p = 0.02) and ≥80 years (2.70, SE 0.99, p = 0.013) compared to the expected trend. Females experienced an increase in antipsychotic incidence in quarter 4 of 2020 (2.41 per 1,000) (**Figure 6A**). In contrast, the incidence of antipsychotic use in the last quarter of 2020 was 1.77 per 1,000 for men. A significant increase in antipsychotic incidence in quarter 4 compared to the



* Statistically significant (p<0.05) increase in Q2 of 2020 for ≥80 years; and Q4 of 2020 for 40-64 years, 65-79 years, ≥80 years

* Statistically significant (p<0.05) increase in Q4 of 2020 for <18 years, 19-39 years, 40-64 years, 65-79 years, ≥80 years; and increase in Q3 of 2020 for 65-79 years and ≥80 years

FIGURE 5 | (A) Antipsychotic incidence by age group (per 1,000). **(B)** Antipsychotic prevalence by age group (per 1,000).



* Statistically significant (p<0.05) increase in Q4 of 2020 for women

* Statistically significant (p<0.05) increase in Q3 of 2020 for women and increase in Q4 of 2020 for men and women

FIGURE 6 | (A) Antipsychotic incidence by sex (per 1,000). **(B)** Antipsychotic prevalence by sex (per 1,000).

expected trend was seen only females (0.52, SE 0.12, $p = 0.0004$). Both males and females experienced an increase in antipsychotic prevalence over time (from 17.84 per 1,000 in the first quarter of 2015 to 21.69 per 1,000 in the last quarter of 2020 for males and 19.57 per 1,000 in the first quarter of 2015 to 24.13 per 1,000 in the last quarter of 2020 for females) (**Figure 6B**). Females had a significantly higher antipsychotic prevalence in Q3 (0.81, SE 0.28, $p = 0.01$) and Q4 (1.47, SE 0.29, $p < 0.0001$) of 2020. Males had a higher antipsychotic prevalence in Q4 of 2020 (0.52, SE 0.25, $p = 0.0459$).

DISCUSSION

In this population-based study in the Canadian province of Manitoba, we observed a significant decrease in the incident use of antidepressants and anxiolytics in most age groups and both sexes immediately (i.e., within the second quarter of 2020) following COVID-19 public health measures, compared to the expected trend. We also observed the incidence of antidepressant and antipsychotic use to be the highest at the end of 2020, compared with the same period in the previous 5 years. Women and those aged 40 years and older (especially aged 80 years and older) had the highest incidence in antidepressant and antipsychotic use at the end of 2020.

A surprising finding was an increase in the incidence of antidepressant and antipsychotic use in the final quarter of 2020 across most age groups and both sexes, but particularly in the 80+ year old and female population. A greater increase in the incidence of antipsychotic use among the older adult population is consistent with a previous Canadian study of nursing home residents (Avery et al., 2021). This study from the Canadian province of Ontario found an increase in the mean monthly proportion of nursing home residents receiving a prescription for an antipsychotic, antidepressant, and trazodone in March to September 2020 compared to January to February 2020 (Stall et al., 2021). Prolonged social isolation and reduced availability of nonpharmacological interventions

may be contributing factors to these trends. However, it was unexpected to see a similar trend in community-dwelling older adults against national surveys reporting mental health to be less affected by the pandemic than for younger populations (Vahia et al., 2020). Our study also found an increase in incidence in antidepressant and antipsychotic use in the final quarter of 2020 for women and not men. Women may experience particular challenges with prolonged public health restrictions. Home schooling, work demands, child care duties could have an impact on the mental health for women over this period, especially by the last quarter of 2020. Previous studies have cited disproportionate levels of major depressive disorder and anxiety among women, particularly those with children (COVID-19 Mental Disorders Collaborators, 2021; Avery et al., 2021). In Manitoba, the College of Physicians released a Standards of Practice for benzodiazepine prescribing in November 1, 2020, which introduced new requirements and limits on benzodiazepine prescribing (The College of Physicians & Surgeons of Manitoba, 2020). It is possible that these new standards may have resulted in the substitution of anxiolytic/sedative-hypnotics with antipsychotics and/or antidepressants in the last quarter of 2020. It is also not known whether the increase in antidepressant use may be a result of long COVID and care providers may be treating post-COVID depression with antidepressants. One study found individuals who have had COVID-19 experienced greater rates of mental health disorders and antidepressant use than those without COVID-19 (Xie et al., 2022). While the number of reported positive COVID-19 cases in Manitoba were low at the beginning of the pandemic, there were 23,625 Manitobans who had COVID-19 by December 2020, and it is not known what proportion of the population had COVID-19 that was not lab-confirmed (Manitoba Government, 2020a).

The declining trend in both the incidence and prevalence of anxiolytic/sedative-hypnotic use is not surprising considering efforts to minimize the long-term use of these agents (The College of Physicians & Surgeons of Manitoba, 2020). The new Standards of Practice for benzodiazepine prescribing in Manitoba could have affected the prescribing of benzodiazepines in the fourth quarter of 2020 (The College of Physicians & Surgeons of Manitoba, 2020). It is important to also note that we would expect to observe a seasonal trend in which a peak incidence would be observed in quarter 1 (January to March) and a trough incidence would be observed in quarter 2 (April to June) of every year. This is because all eligible Manitoba residents receive full coverage on eligible prescription medications after an income-based deductible is paid, which resets to zero on April 1 of every year. However, at the beginning of the pandemic (quarter 2 or April to June of 2020), we would also expect to see a greater decline in the incidence of psychotropic medication use, and anxiolytic/sedative-hypnotics in particular. This was the period shortly after in-person visits were restricted. It is possible that there may be less comfort among prescribers to prescribe new prescriptions for these agents in a virtual environment or people were less inclined to leave their homes to fill a prescription during the pandemic. While another study also found a significant decline in opioid and benzodiazepine prescriptions following restrictions to elective medical procedures and routine office visits (Downs et al., 2021), there are no studies to support whether a change in comfort in prescribing or having prescriptions refilled in-person is occurring among prescribers and patients, respectively. Most pharmacies in Manitoba offer home delivery or curb-side pick-up of prescriptions. Low incidence of psychotropic medication use in the second quarter could also be explained by a lower priority to initiate care following a major global event. However again there are no studies to support that this is a possibility. Other studies have found an increase in the use of psychotropic medications shortly after a major event (Benjamin and Steven, 2004; DiMaggio et al., 2007).

Drug shortages were a concern in the early months of 2020 (Drug Shortages Canada, 2022). Stockpiling of medication could explain the slight elevation in prevalence of benzodiazepines seen in quarter one. Pharmacists in Manitoba were to provide only a 1-month supply in a 28-day period for all drugs to allow access to medications for patients for medications in short supply. However, this restriction was implemented March 20, 2020 (Manitoba Government, 2020b) and was lifted in May 11, 2020 (Manitoba Government, 2020c). This may explain the fluctuations in prescription fills in quarters 1 and 2 of 2020.

Our findings contrasted the results of a cross-sectional study where the investigators found no clinically meaningful differences in overall prescription rates of psychotropic medications in 2020, compared to 2019, using data from Kaiser Permanente Northern California electronic records (Hirschtritt et al., 2021). After accounting for secular trends or prior year patterns, they found a small, but significant increase in the antidepressant trazodone and mood stabilizers/antipsychotics, and a small decrease in benzodiazepines and hypnotics, with no significant change in antidepressants and stimulants (Hirschtritt et al., 2021). They also found a lower-than-expected trend in new fills for nearly all medications, including antidepressants, benzodiazepines, hypnotics, and mood stabilizers and antipsychotics (Hirschtritt et al., 2021). This was consistent with our findings of a decline in incidence in antidepressants and anxiolytic/sedative-hypnotic use in the second quarter as their data were only limited to the first 13 weeks of the pandemic in California. Their study did not examine the long-term effects of the pandemic on these trends nor did they look back beyond 2019 for secular trends. A major limitation of this study was the use of prescription data from a single insurer, which limits the generalizability to the entire population including those without insurance coverage. This is particularly important during a time when job security may have changed because of the pandemic.

A pilot study by Yu et al. including 365 patients from an independent community pharmacy in North York, Ontario found no difference in the initiation of new prescriptions for antidepressants and antianxiety medications during the first few months of the pandemic compared to the prior year ($p = 0.251$) (Yu et al., 2021). This study did find more frequent dispensing of benzodiazepine tablets ($p = 0.016$) in the first 5 months of 2020 compared to the same period in 2019 (Yu et al., 2021). However, no significant differences were observed in the number of defined

daily doses between the two time periods (Yu et al., 2021). This study was limited by its sample size and its data source from one community pharmacy. Uthayakumar et al. similarly found a reduction in antidepressant dispensations in April 2020 but a return to pre-pandemic trends from August to December 2020 (Uthayakumar et al., 2022). This study found no difference in benzodiazepine dispensation before and during COVID-19. This study used data from IQVIA (IMS Health and Quintiles), which captures approximately 78% of prescriptions dispensed in Canada. This study only examined dispensation rates as tablets per 100 population and did not evaluate antipsychotic use.

Strengths of our study included the use of a large administrative database unrestricted by age, income, or insurance coverage. We also examined drug trends to the end of 2020 where previous studies have only examined the first few months of 2020 and we were able to compare to the previous 4 years. Our findings may not be generalizable to populations without universal health care coverage. In addition, DPIN data captures prescriptions received by patients but does not necessarily imply actual consumption of medication. Factors influencing prescription trends are multifactorial (e.g., drug shortages, drug coverage fiscal period, public health restrictions, pandemic) with each factor able to explain the trends observed, therefore it is difficult to pinpoint whether one factor contributed to the observed trends more predominantly than the others. Moreover, the rate of COVID-19 positive patients in Manitoba was low at the beginning of pandemic compared to other jurisdictions during 2020 (273 total COVID-19 positive cases as of April 29, 2020 to 23,625 total number of lab-confirmed cases in Manitoba as of December 24, 2020) (Manitoba Government, 2020a; Manitoba Government, 2020d), and as such it is difficult to generalize findings to locations with higher rates of infection.

This study provided insight on important questions about mental health treatment and consequences related to the pandemic. Findings from this study will help inform decisions around processes of care for mental health.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data used in this article was derived from administrative health and social data as a secondary use. The data was provided under specific data sharing agreements only for approved use at MCHP. The original source data is not owned by the researchers or Manitoba Centre for Health Policy (MCHP) and as such cannot be provided to a public repository. The original data source and approval for use has been noted in the acknowledgments of the article. Where necessary, source data specific to this article or project may be reviewed at MCHP with the consent of the original data providers, along with the required privacy and ethical review bodies. Requests to access these datasets should be directed to mchp_access@cpe.umanitoba.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human Research Ethics Board of the University of Manitoba. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This study was funded by the Research Manitoba COVID-19 Rapid Response Grant.

ACKNOWLEDGMENTS

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project HIPC 2020/2021-29. Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba, and were derived from data provided by Manitoba Health and Vital Statistics and Winnipeg Regional Health Authority/Shared Health.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.886652/full#supplementary-material

REFERENCES

Avery, A. R., Tsang, S., Seto, E. Y. W., and Duncan, G. E. (2021). Differences in Stress and Anxiety Among Women with and without Children in the Household During the Early Months of the COVID-19 Pandemic. *Front. Public Health* 9, 688462. doi:10.3389/fpubh.2021.688462 Available at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.688462/full (Accessed February 4, 2022).

Benjamin, D., and Steven, M. (2004). Use of Psychotropic Medications Before and After Sept. 11, 2001. *Am. J. Psychiatry* 161 (8), 1377–1383.

Brownell, M., Chartier, M., Au, W., MacWilliam, L., Schultz, J., Guenette, W., et al. (2015). *The Educational Outcomes of Children in Care in Manitoba*. Winnipeg, MB: Manitoba Centre for Health Policy.

Brownell, M., Chartier, M., Santos, R., Ekuma, O., Au, W., Sarkar, J., et al. (2012). *How Are Manitoba's Children Doing? Winnipeg*. MB: Manitoba Centre for Health Policy.

Canadian Centre on Substance Use and Addiction (2020). COVID-19 and Increased Alcohol Consumption: NANOS Poll Summary Report. Submission 2020-1621.

Available at: https://www.ccsa.ca/covid-19-and-increased-alcohol-consumption-nanos-poll-summary-report (Accessed May 7, 2020).

Canadian Mental Health Association National Survey (2020). CAMH COVID-19 National Survey 2020. Available at: https://www.camh.ca/en/health-info/mental-health-and-covid-19/covid-19-national-survey (Accessed February 1, 2022).

Centre for Addiction and Mental Health (2020). COVID-19 Pandemic Adversely Affecting Mental Health of Women and People with Children. Available at: https://www.camh.ca/en/camh-news-and-stories/covid-19-pandemic-adversely-affecting-mental-health-of-women-and-people-with-children.

Chartier, M., Dart, A., Tangri, N., Komenda, P., Walld, R., Bogdanovic, B., et al. (2015). *Care of Manitobans Living with Chronic Kidney Disease*. Winnipeg, MB: Manitoba Centre for Health Policy.

Covid-19 Mental Disorders Collaborators (2021). Global Prevalence and Burden of Depressive and Anxiety Disorders in 204 Countries and Territories in 2020 Due to the COVID-19 Pandemic. *Lancet* 398 (10312), P1700–P1712.

Daumit, G. L., Crum, R. M., Guallar, E., Powe, N. R., Primm, A. B., Steinwachs, D. M., et al. (2003). Outpatient Prescriptions for Atypical Antipsychotics for African Americans, Hispanics, and Whites in the United States. *Arch. Gen. Psychiatry* 60 (2), 121–810. doi:10.10001/archpsyc.60.2.121

DiMaggio, C., Galea, S., and Madrid, P. A. (2007). Population Psychiatric Medication Prescription Rates Following a Terrorist Attack. *Prehosp. Disaster Med.* 22 (6), 479–484. doi:10.1017/s1049023x0000529x

Downs, C. G., Varisco, T. J., Bapat, S. S., Shen, C., and Thornton, J. D. (2021). Impact of COVID-19 Related Policy Changes on Filling of Opioid and Benzodiazepine Medications. *Res. Soc. Adm. Pharm.* 17 (1), 2005–2008. doi:10.1016/j.sapharm.2020.06.003

Drug Shortages Canada (2022). Drug Shortages Canada. Available at: https://www.drugshortagescanada.ca/ (Accessed February 4, 2022).

Grekou, D., and Lu, Y.Statistics Canada (2021). Gender Differences in Employment One Year into the COVID-19 Pandemic: An Analysis by Industrial Sector and Firm Size. *Econ. Soc. Rep.* 1 (5), 2563–8955. Available at: https://www150.statcangc.ca/n1/pub/36-28-0001/2021005/article/00005-eng.htm.

Gunnell, D., Appleby, L., Arensman, E., Hawton, K., John, A., Kapur, N., et al. (2020). Suicide Risk and Prevention During the COVID-19 Pandemic. *Lancet Psychiatry* 7 (6), 468–471. doi:10.1016/S2215-0366(20)30171-1

Hirschtritt, M. E., Slama, N., Sterling, S. A., Olfson, M., and Iturralde, E. (2021). Psychotropic Medication Prescribing During the COVID-19 Pandemic. *Medicine (Baltimore)* 100 (43), e27664. doi:10.1097/MD.0000000000027664

Holmes, E. A., O'Connor, R. C., Perry, V. H., Tracey, I., Wessely, S., Arseneault, L., et al. (2020). Multidisciplinary Research Priorities for the COVID-19 Pandemic: a Call for Action for Mental Health Science. *Lancet Psychiatry* 7 (6), 547–560. doi:10.1016/S2215-0366(20)30168-1

Kokou-Kpolou, C. K., Megalakaki, O., Laimou, D., and Kousouri, M. (2020). Insomnia During COVID-19 Pandemic and Lockdown: Prevalence, Severity, and Associated Risk Factors in French Population. *Psychiatry Res.* 290, 113128. doi:10.1016/j.psychres.2020.113128

Li, Y., Qin, Q., Sun, Q., Sanford, L. D., Vgontzas, A. N., and Tang, X. (2020). Insomnia and Psychological Reactions During the COVID-19 Outbreak in China. *J. Clin. Sleep Med.* 16, 1417–141810. doi:10.5664/jcsm.8524

Manitoba Government (2020b). COVID-19 Bulletin #23. Available at: https://news.gov.mb.ca/news/index.html?archive=&item=47139 (Accessed February 4, 2022).

Manitoba Government (2020a). COVID-19 Bulletin #295. December 24. Available at: http://news.gov.mb.ca/news/print,index.html?item=50107 (Accessed March 20, 2022).

Manitoba Government (2020c). COVID-19 Bulletin #77. Available at: https://news.gov.mb.ca/news/index.html?item=48019&posted=2020-05-08 (Accessed February 4, 2022).

Manitoba Government (2020b). COVID-19 Novel Coronavirus COVID Response Update. Available at: https://manitoba.ca/asset_library/en/proactive/2020_2021/manitoba_response_april2020.pdf (Accessed February 18, 2022).

Mchp Concept Dictionary (2016). Mental Disorder/Mental Health Disorder/Mental Health Illness Classification. Available at: http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1182 (Accessed May 7, 2020).

Mental Health Commission of Canada and Canadian Centre (2021). Mental Health Commission of Canada and Canadian Centre on Substance Use and Addiction Poll. Available at: www.ccsa.ca/covid-19-stress-amplifying-mental-health-and-substance-use-concenrs-leger-poll (Accessed February 17, 2021).

Roos, L. L., Gupta, S., Soodeen, R. A., and Jebamani, L. (2005). Data Quality in an Information-Rich Environment: Canada as an Example. *Can. J. Aging* 24 (1), 153–170. doi:10.1353/cja.2005.0055

Roos, L. L., and Nicol, J. P. (1999). A Research Registry: Uses, Development, and Accuracy. *J. Clin. Epidemiol.* 52, 39–47. doi:10.1016/s0895-4356(98)00126-7

Smith, M., Finlayson, G., Martens, P., Dunn, J., Prior, H., Taylor, C., et al. (2013). *Social Housing in Manitoba. Part II: Social Housing and Health in Manitoba: A First Look*. Winnipeg, MB: Manitoba Centre for Health Policy.

Stall, N. M., Zipursky, J. S., Rangrej, J., Jones, A., Costa, A. P., Hillmer, M. P., et al. (2021). Assessment of Psychotropic Drug Prescribing Among Nursing Home Residents in Ontario, Canada, During the COVID-19 Pandemic. *JAMA Intern. Med.* 181 (6), 861–863. doi:10.1001/jamainternmed.2021.0224

Statsitics Canada (2021). Impact of the COVID-19 Pandemic on Canadian Seniors. Available at: https://www150.statcangc.ca/n1/pub/75-006-x/20211001/article/00009-eng.htm.

The College of Physicians & Surgeons of Manitoba (2020). Standard of Practice. Prescribing Benzodiazepines & Z-Drugs (Including Zopiclone & Other Drugs). Available at: https://cpsm.mb.ca/assets/Standards%20of%20Practice/Standard%20of%20Practice%20Prescribing%20Benzodiazepines%20and%20Z-Drugs.pdf (Accessed February 4, 2022).

The Covid-19 Healthcare Coalition Telehealth Impact Study Work Group (2020). Telecare Impact: Physician Survey Analysis. COVID-19 Healthcare Coalition. Available at: https://c19hcc.org/telehealth/physciian-survey-analysis.

Thibaut, F., and van Wijngaarden-Cremers, P. J. M. (2020). Women's Mental Health in the Time of Covid-19 Pandemic. *Front. Glob. Womens Health* 1, 588372. doi:10.3389/fgwh.2020.588372

Uthayakumar, S., Tadrous, M., Vigod, S. N., Kitchen, S. A., and Gomes, T. (2022). The Effects of COVID-19 on the Dispensing Rates of Antidepressants and Benzodiazepines in Canada. *Depress. Anxiety* 39 (2), 156–162. doi:10.1002/da.23228

Vahia, I. V., Jeste, D. V., and Reynolds, C. F. (2020). Older Adults and the Mental Health Effects of COVID-19. *JAMA* 324 (22), 2253–2254. doi:10.1001/jama.2020.21753

Vigo, D., Patten, S., Pajer, K., Krausz, M., Taylor, S., Rush, B., et al. (2020). Mental Health of Communities During the COVID-19 Pandemic. *Can. J. Psychiatry* 65 (10), 681–687. doi:10.1177/0706743720926676

Vindegaard, N., and Benros, M. E. (2020). COVID-19 Pandemic and Mental Health Consequences: Systematic Review of the Current Evidence. *Brain Behav. Immun.* 89, 531–54210. doi:10.1016/j.bbi.2020.05.048

Voitsidis, P., Gliatas, I., Bairachtari, V., Papadopoulou, K., Papageorgiou, G., Parlapani, E., et al. (2020). Insomnia During the COVID-19 Pandemic in a Greek Population. *Psychiatry Res.* 289, 113076. doi:10.1016/j.psychres.2020.113076

World Health Organization (2021). Anatomical Therapeutic Chemical Classification. Available at: https://www.who.int/tools/atc-ddd-toolkit/atc-classification (Accessed March 16, 2022).

Xie, Y., Xu, E., and Al-Aly, Z. (2022). Risks of Mental Health Outcomes in People with Covid-19: Cohort Study. *Bmj* 376, e068993. doi:10.1136/bmj-2021-068993

Yu, C., Boone, C., Askarian-Monavvari, R., and Brown, T. (2021). Trends in Pharmacotherapy for Anxiety and Depression During COVID-19: A North York Area Pilot Study. *Univ. Toronto Med. J.* 98 (1), 41–46.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Pharmacology

BRIEF RESEARCH REPORT
published: 04 May 2022
doi: 10.3389/fphar.2022.855598

Electronic Health Records to Rapidly Assess Biosimilar Uptake: An Example Using Insulin Glargine in a Large U.S. Nursing Home Cohort

Kaleen N. Hayes[1]*, *Vincent Mor*[1,2] and *Andrew R. Zullo*[1,2,3]

[1]Department of Health Services, Policy and Practice, Brown University School of Public Health, Providence, RI, United States, [2]Center of Innovation in Long-Term Services and Supports, Providence VA Medical Center, Providence, RI, United States, [3]Department of Epidemiology, Brown University School of Public Health, Providence, RI, United States

Large healthcare administrative databases, like Medicare claims, are a common means to evaluate drug policies. However, administrative data often have a lag time of months to years before they are available to researchers and decision-makers. Therefore, administrative data are not always ideal for timely policy evaluations. Other sources of data are needed to rapidly evaluate policy changes and inform subsequent studies that utilize large administrative data once available. An emerging area of interest in both pharmacoepidemiology and drug policy research that can benefit from rapid data availability is biosimilar uptake, due to the potential for substantial cost savings. To respond to the need for such a data source, we established a public-private partnership to create a near-real-time database of over 1,000 nursing homes' electronic health records to describe and quantify the effects of recent policies related to COVID-19 and medications. In this article, we first describe the components and infrastructure used to create our EHR database. Then, we provide an example that illustrates the use of this database by describing the uptake of insulin glargine-yfgn, a new exchangeable biosimilar for insulin glargine, in US nursing homes. We also examine the uptake of all biosimilars in nursing homes before and after the onset of the COVID-19 pandemic. We conclude with potential directions for future research and database infrastructure.

Keywords: health policy, pharmacoepidemiology, nursing homes, diabetes mellitus, insulin, big data, biological products

OPEN ACCESS

Edited by:
Carlos Alves,
University of Coimbra, Portugal

Reviewed by:
Tanja Mueller,
University of Strathclyde, United Kingdom
Pooyeh Graili,
University of Toronto, Canada

****Correspondence:***
Kaleen N. Hayes
kaley_hayes@brown.edu

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: *15 January 2022*
Accepted: *18 April 2022*
Published: *04 May 2022*

Citation:
Hayes KN, Mor V and Zullo AR (2022) Electronic Health Records to Rapidly Assess Biosimilar Uptake: An Example Using Insulin Glargine in a Large U.S. Nursing Home Cohort. Front. Pharmacol. 13:855598. doi: 10.3389/fphar.2022.855598

INTRODUCTION

Drug policies are critical to ensure that cost-effective and safe medications are used in clinical practice. Policies are most commonly implemented by payors and often take the form of formulary tiers and restrictions (Health Affairs, 2017) but may include direct mandates, incentive payments, and other mechanisms. Drug policies must be evaluated, often *via* pharmacoepidemiologic or economic studies, to ensure that the policies result in desired effects and do not have loopholes, inequities, or unintended consequences (European Monitoring Centre for Drugs and Drug Addiction, 2017).

A major area in drug policy is the use of biosimilars (Stern et al., 2021). Biologic medications make up approximately half of the expenditures for the top 25 drugs in the US and Canada (Tadrous et al., 2021; Tichy et al., 2021), with increasing costs each year. Thus, biosimilar use has the potential to result in substantial healthcare cost reductions. As of January 2022, 33 biosimilars have been

approved for use in the US (U.S. Food & Drug Administration, 2021a), yet timely study of the uptake of biosimilars and related policies has been limited, especially for vulnerable populations like older adults and nursing home (NH) residents. Presently, some states allow biosimilars to be interchanged without notifying the prescriber or patient. Others require notification of the prescriber and/or patient. Yet others require that the prescriber specify that substitution is permissible (Cauchi, 2019). Thus, automatic substitution may not be consistently implemented across the US, but data are limited. A primary barrier to the timely evaluation of biosimilar uptake is a lag in the availability of healthcare administrative data (e.g., Medicare claims or national spending data). Rapid availability of data is critical to evaluate the uptake of biosimilars as they come to market and the impact of biosimilar-related policies on this uptake.

Insulin glargine-yfgn (Semglee®) was approved as an insulin product in the US on 11 June 2021 (U.S. Food & Drug Administration, 2021b), then as the first interchangeable biosimilar product for insulin glargine (Lantus®) on 28 July 2021 (U.S. Food & Drug Administration, 2021a; U.S. Food & Drug Administration, 2021c). Insulin glargine-yfgn could be directly prescribed as soon as it came to market if explicitly written for by the prescriber [similar to the other brand name insulin glargine (Basaglar®)]. However, after biosimilar approval insulin glargine-yfgn could be *directly interchanged* for insulin glargine (Lantus®) prescriptions at the point of dispensing by the pharmacy without prescriber approval, similar to the process of generic medication substitutions (U.S. Food & Drug Administration, 2017). Insulin biosimilars have the potential for substantial impact on healthcare cost savings; insulin glargine was the 3rd top drug in expenditures (USD 9.7 billion) in the US in 2020 (Tichy et al., 2021). List price (without accounting for rebate programs, coupons, discounts, or wholesale pricing) for a 10 ml vial of insulin glargine-yfgn is USD 126 (GoodRx, 2022b); in contrast, the reference insulin glargine product is listed at USD 315 per vial (GoodRx, 2022a). Further, another biosimilar for insulin glargine (insulin glargine-aglr) was recently approved on 17 December 2021 (U.S. Food & Drug Administration, 2021a).

In US NHs alone, costs related to diabetes care exceeded $19.6 billion in 2012 (American Diabetes Association, 2013), with over one-third of residents having diabetes (Resnick et al., 2008; Dybicz et al., 2011; Newton et al., 2013). Fifty-nine percent of NH residents with diabetes are treated with insulin (Newton et al., 2013; Zullo et al., 2016a; Zullo et al., 2016b). Understanding early uptake of insulin biosimilars in NHs, where diabetes and insulin use are prevalent, may help to anticipate the trajectory of use in other clinical settings in the US while also providing due attention to a vulnerable population.

METHODS

Overview of Data Sources

In mid-2020 we began a partnership to leverage data from 12 NH chains with a common EHR system (PointClickCare®) to answer stakeholder questions related to COVID-19 infection and vaccinations (White et al., 2020; Bardenheier et al., 2021a; White et al., 2021a; Bardenheier et al., 2021b; White et al., 2021b; White and Mor, 2021). These chains comprise more than 1,100 facilities located in almost every state in the contiguous US, with approximately 75,100 total beds. Residents of these facilities include both long-term NH residents as well as individuals undergoing post-acute care skilled nursing facility (SNF) stays. The residents of these chains are approximately representative of all individuals who reside in NH facilities nationally.

The NH EHR records contain information on the daily census (person-level file that contains each resident's disposition on a given day, including transfers, discharges, and deaths), resident demographics (e.g., age, sex, race/ethnicity), nurses' change in condition notes, immunization records, laboratory data, vital signs (e.g., blood pressure, temperatures) diagnosis codes, medication orders (medication initiation and discontinuation), non-medication orders (e.g., procedures, diagnostic testing, advance directives) and the electronic medication administration record (eMAR, contains an order number for each administration). In addition, the EHR contains Minimum Data Set (MDS) assessments, federally mandated clinical evaluations that must be conducted at admission for all NH residents and at least quarterly thereafter during their stay in the NH. Assessments include demographics, a 28-point scale of Activities of Daily Living (ADL) performance, a cognitive function assessment, and indicators of chronic comorbidities (e.g., diabetes). All datasets contain person-level information.

EHR data are transferred from PointClickCare® directly to our secure, encrypted server infrastructure. Access to the server network is highly controlled and internet access on the server is limited. Each component of the EHR (e.g., census, orders, eMAR, etc.) is transferred in a separate dataset for each chain and is only accessible in identifiable format by one data specialist. The data specialist then runs SAS programs to anonymize, clean, and process the data into SAS datasets, including macros to derive useful variables and "cross walks" to ensure data validity (e.g., the order identifier for a medication in the eMAR matches a corresponding order in the orders dataset). A chain-wide, anonymized patient identifier is generated based on each chain's patient identifiers and can be used to link datasets. Brown University's Institutional Review Board approved the study and waived the requirement for informed consent.

Example: Insulin Glargine-Yfgn and General Biosimilar Uptake

We identified all NH residents (regardless of length of stay) with evidence of biosimilar use between 1 January 2018 and 30 November 2021 *via* medication orders in the EHR. A full list of eligible biosimilars is provided in **Supplementary Table S1**). Both generic and brand names for the biosimilar products were used to identify use. For the insulin glargine-yfgn analysis, we restricted this cohort to all individuals with use of insulin glargine-yfgn (defined as at least one record of administration in the eMAR) between 11 June 2021 (date of official approval by

the FDA as an insulin product) and 30 November 2021 (the most recent data available at the time of analysis). We chose to define insulin glargine-yfgn use as at least one administration because we wanted to examine any uptake, rather than multiple administrations that represent a period of extended use. Nevertheless, we assessed the number of administrations of insulin glargine-yfgn for each resident to examine whether initial uptake was followed by sustained use. To understand the degree of use among all residents on any basal insulin regimen, we then calculated the monthly rate of residents with insulin glargine-yfgn use per 1,000 residents with any basal insulin use (intermediate-acting or long-acting insulins: insulin glargine [Lantus®, Basaglar®, or Semglee®], NPH, degludec, or detemir. To quantify changes over time, we divided the rate of residents with insulin glargine-yfgn use in November 2021 by the rate in June 2021 and estimated a parametric Wald 95% confidence interval (CI) for this value.

Next, we estimated the proportion of residents who switched from a non-glargine-yfgn basal insulin to insulin glargine-yfgn and, among these, time since first basal insulin use to glargine-yfgn use. We also calculated the time since admission to the NH to insulin glargine-yfgn initiation for all residents. Using lookback data in the 6 months prior to first insulin glargine-yfgn use for each resident, we described resident demographics and basic clinical characteristics using data from the MDS for residents with at least one MDS assessment of any type. We presented characteristics among all residents with insulin glargine-yfgn use and also stratified by whether the individual initiated insulin glargine-yfgn before versus after it was approved as an exchangeable biosimilar.

For the general biosimilar uptake analysis, we quantified the number of unique residents with biosimilar use for each month of the study. We graphed trends over time in all biosimilar use and use of insulin glargine-yfgn versus other biosimilars. We examined whether biosimilar use changed after the onset of the COVID-19 pandemic using an interrupted time series (ITS) analysis with segmented linear regression models. The ITS quantified the linear trend in the number of unique biosimilar users over time, the immediate effect of the onset of the pandemic (March 2020), and the effect of the onset of the pandemic on the linear trend in use over time. Because preliminary results showed a very little biosimilar use in 2018 and a drastic increase in biosimilar use when insulin glargine-yfgn came to market in June 2021, the ITS analysis used data from January 2019 to May 2021. Finally, we estimated the proportion of unique residents with orders for each type of biosimilar. SAS version 9.4 and STATA version 17 were used to conduct all analyses (SAS Institute, Cary, NC, United States; StataCorp, College Station, TX, United States).

RESULTS

Insulin Glargine-Yfgn Uptake

We identified 1,567 unique NH residents who initiated insulin glargine-yfgn with 74,764 total recorded administrations in the eMAR. The median number of insulin glargine-yfgn administrations per resident was 27 (25th percentile: 12; 75th percentile: 60), and 97% of residents had more than one administration. In total, 1,554 (>99%) of these residents had at least one MDS assessment to provide characteristics. Residents initiating insulin glargine-yfgn had a median age of 68 years (25th percentile: 60; 75th percentile 76), 68% were White, 54% were male, and 54% switched from another basal insulin. The rate of individuals initiating insulin glargine-yfgn among all of those with any basal insulin use increased over time, from 34.3 residents using insulin glargine-yfgn for every 1,000 on basal insulin in June 2021 to 65.4 per 1,000 in November (**Figure 1**). This change over time represented a 1.90-fold increase (95% CI: 1.56–2.44). The rate of new initiators was greatest in June 2021 (34.3 per 1,000). Rates thereafter remained relatively stable, between approximately 20–26 new users per 1,000 on basal insulin. Among the 1,554 residents with an MDS assessment, 564 (37%) initiated insulin glargine-yfgn before biosimilar approval (**Table 1**). Compared to individuals whose first insulin glargine-yfgn use occurred after biosimilar approval, those with use prior had been in the NH for longer on average (median 17 versus 2 days) and more had use of another basal insulin prior to insulin glargine-yfgn (71% versus 44%). Age, sex, and race/ethnicity distributions were similar between groups. **Supplementary Table S2** shows standardized mean differences that compare the distribution of characteristics between individuals starting insulin glargine-yfgn before versus after biosimilar approval.

General Biosimilar Use

Overall, the use of biosimilars was low (**Figure 2**). We identified 3,608 unique NH residents with biosimilar use. Less than 50 total individuals had any evidence of use in 2018. Residents on epoetin products made up the majority (52%), with insulin glargine-yfgn use as the second most common (43%). Filgrastim was the next most common (4.1% of residents), with all other biosimilars comprising less than 1% of use. The ITS analysis estimated a small but significant increase in the number of biosimilar users over time (average 7 [95% CI 5 to 9; $p < 0.001$] additional new users per month). The onset of the COVID-19 pandemic was associated with an immediate decrease in biosimilar use (effect of the pandemic: 38 fewer users [95% CI -57 to -18; $p = 0.001$]). However, the pandemic did not result in a significantly different trend in use over time leading up to when insulin glargine-yfgn came to market in June 2021 (interaction effect of pandemic*time: 2 fewer patients per month [95% CI -4 to 1; $p = 0.32$]).

DISCUSSION

We leveraged a first-of-its-kind, near-real-time database of EHR records to evaluate the uptake of biosimilars since 2018 among a large population of US NH residents. Biosimilar use decreased immediately at the onset of the COVID-19 pandemic. This finding is unsurprising given the extreme stresses placed on NH like outbreaks, staffing shortages, and competing clinical

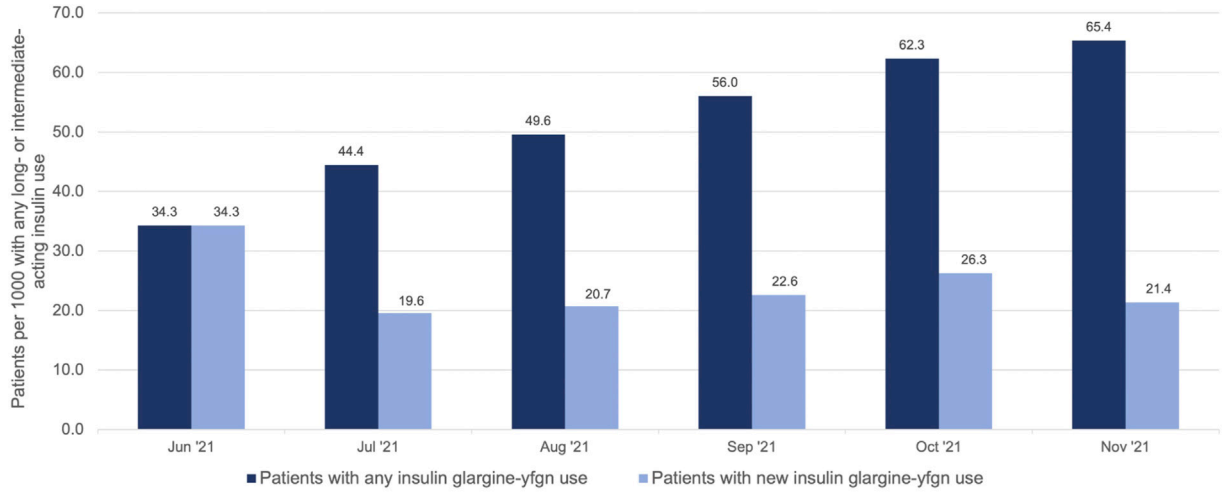


FIGURE 1 | Number of nursing home residents with use of insulin glargine-yfgn (Semglee®) per 1,000 on any basal (long- or intermediate-acting) insulin use*, 2021.
**includes insulin glargine [Lantus®, Basaglar®, or Semglee®], NPH, degludec, or detemir.*

TABLE 1 | Characteristics of nursing home residents initiating insulin glargine-yfgn before versus after biosimilar approval, United States, 2018–2021.

	All Initiators[a] (*N* = 1,554) n (%)[b]	Initiated prior to biosimilar approval (*N* = 564)[a] n (%)[b]	Initiated after biosimilar approval (N = 990)[a] n (%)[b]
Age, years (median [Q1, Q3])	68 (60, 76)	68 (60, 75)	68 (59, 76)
Male	833 (53.6)	311 (55.1)	522 (52.7)
Race/Ethnicity[c]			
White	1,051 (67.6)	382 (67.7)	669 (67.6)
Black	351 (22.6)	131 (23.2)	220 (22.2)
Hispanic	37 (2.4)	15 (2.7)	22 (2.2)
Asian, Pacific Islander, or Indigenous/Native American	16 (1.0)	8 (1.4)	8 (0.8)
Other/Missing	107 (6.9)	30 (5.3)	77 (7.8)
Time from first NH admission to first insulin glargine-yfgn use, days [median (Q1, Q3)]	2 (1, 35)	17 (1, 103)	2 (1, 9)
History of prior basal insulin use	833 (53.6)	401 (71.1)	432 (43.6)
Time since first basal insulin use, days (median [Q1, Q3])	33 (2, 401)	45 (7, 401)	15 (1, 397)
Renal impairment	282 (18.2)	144 (25.5)	138 (13.9)
Asthma or chronic obstructive pulmonary disease	220 (14.2)	117 (20.7)	103 (10.4)
Arrhythmias	127 (8.2)	73 (12.9)	54 (5.5)
Coronary artery disease	178 (11.5)	103 (18.3)	75 (7.6)
Dementia or Alzheimer's disease	113 (7.3)	63 (11.2)	50 (5.1)
Diabetes	626 (40.3)	336 (59.6)	290 (29.3)
Heart failure	198 (12.7)	109 (19.3)	89 (9.0)
Hypertension	520 (33.5)	288 (51.1)	232 (23.4)
History of stroke or transient ischemic attack	100 (6.4)	51 (9.0)	49 (5.0)

Q1—25th percentile; Q3—75th percentile.
[a]*With at least 1 MDS, Assessment of any type (admission, quarterly, or other); over 99% of all individuals with use.*
[b]*Unless otherwise indicated.*
[c]*Residents could be categorized into multiple race/ethnicity groups.*

priorities combined with drug supply chain shortages. However, the trend in biosimilar use over time was not dramatically impacted by the pandemic. Further, the use of insulin glargine-yfgn appeared to increase over time. We observed an increase in the rate of insulin glargine biosimilar users from June to November 2021, with around one in 20 residents on basal insulin transitioning to glargine-yfgn by the end of the study period. Individuals with insulin glargine-yfgn use also made up 43% of all residents with biosimilar use, despite it being available for just 5 months of the 35-months study period.

This rapid uptake of insulin glargine-yfgn in NH compared to most other biosimilars may result from several concurrent phenomena. First, prescribers in NHs or the pharmacies that serve NHs may be encouraged to use biosimilars for medications administered during a post-acute care SNF stay. During post-acute stays, NHs receive bundled "per diem"

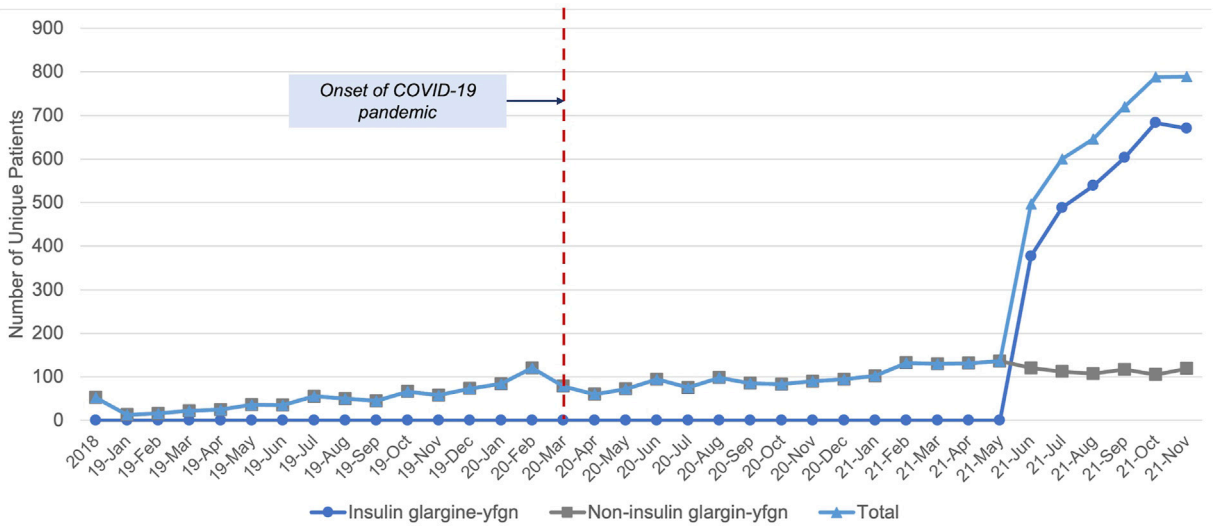


FIGURE 2 | Nursing home residents with biosimilar use over time, 2018–2021.

payments for services provided, including medications, through the Medicare Part A SNF benefit (Congressional Research Service, 2016; Centers for Medicare and Medicaid Services, 2021). Cost-saving measures for drugs are therefore important in this period because the NH can incur a financial loss for the care provided if drugs consume too much or all of the fixed payment. Indeed, residents who started insulin glargine-yfgn after biosimilar approval had a median of 2 days in the facility (versus 17 in those starting before). These residents may have been on basal insulin prior to admission, and thus biosimilar use was a cost-reduction measure to continue this therapy during the SNF benefit period, rather than switching to a less appropriate but cheaper therapy like sliding-scale insulin (Munshi et al., 2016) or withholding the medication entirely.

Conversely, long-stay NH residents (generally defined as >100 days in-facility) have their medications covered *via* claims through Medicare Part D (Centers for Medicare and Medicaid Services, 2021). The Centers for Medicare and Medicaid Services has yet to implement substantive policies to encourage biosimilar use, so there is less financial incentive to use biosimilars among those covered through Part D. Potential policies may include specialty tier pricing or incentives (e.g., higher renumeration for the administration of biosimilar vs reference products). Indeed, limited drug reimbursements during SNF stays may serve as such an incentive in NHs, suggesting cost-savings for the provider or facility are a viable mechanism to increase biosimilar uptake. Future research should compare uptake of insulin biosimilars between the NH, community, and hospital settings.

Many other biologic therapies are administered less frequently than daily insulin (e.g., adalimumab, administered subcutaneously every 2 weeks (AbbVie Pharmaceuticals, 2018)). Thus, the low use of other biosimilars may result in part from use being unnecessary or delayed until discharge or the start of Part D coverage. In fact, epoetin and filgrastim biosimilars were the most common therapies used apart from insulin glargine-yfgn. Epoetin and filgrastim are administered up to three times per week and daily, respectively, suggesting that more frequently administered biologic therapies will have a higher uptake in NH due to required use during SNF stays. Insulin glargine-yfgn is available as a pen containing 300 units of insulin (Mylan Pharmaceuticals, 2021), so ease of administration may also increase its appeal. Finally, provider awareness may have been affected by targeted marketing efforts in NHs due to the large burden of diabetes among residents. Those who started insulin glargine-yfgn prior to its approval as a biosimilar were in-facility longer and had a higher prevalence of previous use of basal insulin; these individuals may have been long-stay residents that were switched by the prescriber from another basal insulin to insulin glargine-yfgn because of facility protocols or prescriber awareness. In contrast, those who initiated after biosimilar approval may have been started on the biosimilar version through automatic substitution by the long-term care pharmacy and were perhaps more likely to be short-stay (e.g., post-acute care SNF stay) residents.

The EHR data do have notable limitations. First, we are not able to consistently capture infusions or other medications administered *outside* the NH facility. Instead, we were required to rely on order fields that contained the medication names of interest and assumed the resident was receiving these treatments. Medication order fields for these drugs generally directed use at an outside provider (e.g., "Resident to visit Dr. X for infusion of rituximab-arrx"). Thus, uptake of biosimilars administered *via* infusions may be substantially greater than what we were able to observe. However, data were not limited by missing claims for Medicare Part B physician-administered medications as with traditional Medicare claims. Further, insulins are administered within the NH and thus are captured consistently in the eMAR. Second, we examined the

uptake of insulin glargine-yfgn in a short period directly before and after biosimilar approval. Results are not necessarily representative of future prescribing behavior, which may be influenced by changes in practice and pricing developments. Third, unlike claims data, which are adjudicated by a payor and have been studied more for validity (e.g., studies validating diagnostic code algorithms), our data are generated in the course of usual care and have not yet been extensively validated. Further study should compare EHR and claims data to investigate whether there is substantial alignment in medication use as measured through these different sources. Finally, though our EHR database is, to our knowledge, the largest for a private-sector (i.e., non-Veterans Affairs) population of NH residents, a larger sample size will help to form better-powered studies of drug effects. Future work will expand these data to NH with other EHR vendors to increase sample size for pharmacoepidemiologic studies.

In conclusion, though stakeholder partnerships and infrastructure were required, we created a database of EHR information for NH residents. This database has proven valuable for rapid investigations during the COVID-19 pandemic; however, this detailed information is also well-suited for timely drug policy evaluations. For example, we illustrated that the biosimilar product insulin glargine-yfgn has had increasing uptake in NHs through 2021, potentially due to cost-savings for the NHs and parent NH companies. Future work could use these data or a similar data source to conduct pharmacoepidemiologic designs that take advantage of medication administration data, such as studies evaluating policies related to medication deprescribing.

DATA AVAILABILITY STATEMENT

The data analyzed in this study was obtained from Brown University, the following licenses/restrictions apply: data use agreement. Requests to access these datasets should be directed to Kaleen Hayes, kaley_hayes@brown.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Brown University Institutional Review Board. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

KH conceptualized this manuscript. KH conducted all analyses, drafted and revised this manuscript and provided final approval of this manuscript. AZ contributed to conception, design, and interpretation of the work; revised this manuscript; and provided final approval of this manuscript. VM acquired funding for this manuscript; contributed to conception, design, and interpretation of the work; revised this manuscript; and provided final approval of this manuscript.

FUNDING

This work was supported by the grants from the National Institute on Aging (3U54AG063546-02S6 and R21AG061632).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.855598/full#supplementary-material

REFERENCES

AbbVie Pharmaceuticals Inc. (2018). HUMIRA® (Adalimumab) Injection, for Subcutaneous Use. Highlights of Prescribing Information. Published online December. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125057s410lbl.pdf (Accessed January 13, 2022).

American Diabetes Association (2013). Economic Costs of Diabetes in the U.S. In 2012. *Diabetes Care* 36 (4), 1033–1046. doi:10.2337/dc12-2625

Bardenheier, B. H., Gravenstein, S., Blackman, C., Gutman, R., Sarkar, I. N., Feifer, R. A., et al. (2021). Adverse Events Following mRNA SARS-CoV-2 Vaccination Among U.S. Nursing home Residents. *Vaccine* 39 (29), 3844–3851. doi:10.1016/j.vaccine.2021.05.088

Bardenheier, B. H., Gravenstein, S., Blackman, C., Gutman, R., Sarkar, I. N., Feifer, R. A., et al. (2021). Adverse Events Following One Dose of mRNA COVID-19 Vaccination Among US Nursing Home Residents with and without a Previous SARS-CoV-2 Infection. *J. Am. Med. Directors Assoc.* 22 (21), 222800763–222822325. doi:10.1016/j.jamda.2021.08.024

Cauchi, R. State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars. Published online May 3, 2019. Available at: https://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx (Accessed January 14, 2021).

Centers for Medicare and Medicaid Services. Drug Coverage under Different Parts of Medicare. Published online July 2021. Available at: https://www.cms.gov/outreach-and-education/outreach/partnerships/downloads/11315-p.pdf (Accessed January 10, 2022).

Congressional Research Service (2016). Medicare Skilled Nursing Facility (SNF) Payments. Published online July 20, 2016. Available at: https://crsreports.congress.gov/product/pdf/R/R42401 (Accessed January 13, 2022).

Dybicz, S. B., Thompson, S., Molotsky, S., and Stuart, B. (2011). Prevalence of Diabetes and the burden of Comorbid Conditions Among Elderly Nursing home Residents. *Am. J. Geriatr. Pharmacother.* 9 (4), 212–223. doi:10.1016/j.amjopharm.2011.05.001

European Monitoring Centre for Drugs and Drug Addiction (2017). *Evaluating Drug Policy: A Seven-step Guide to Support the Commissioning and Managing of Evaluations*. Lisbon, Portugal: Publ Off Eur Union Luxemb. doi:10.2810/107573

GoodRx (2022a). *Insulin Glargine*. GoodRx. Published March 2022. Available at: https://www.goodrx.com/lantus (Accessed March 22, 2022).

GoodRx (2022b). *Insulin Glargine*. GoodRx. Published March 2022. Available at: https://www.goodrx.com/semglee (Accessed March 22, 2022).

Health Affairs (2017). "Formularies," Health Affairs Health Policy Brief. doi:10.1377/hpb20171409.000177

Munshi, M. N., Florez, H., Huang, E. S., Kalyani, R. R., Mupanomunda, M., Pandya, N., et al. (2016). Management of Diabetes in Long-Term Care and Skilled Nursing Facilities: A Position Statement of the American

Diabetes Association. *Diabetes Care* 39 (2), 308–318. doi:10.2337/dc15-2512

Mylan Pharmaceuticals Inc. (2021). SEMGLEE® (Insulin Glargine-Yfgn) Injection, for Subcutaneous Use. Highlights of Prescribing Information. Published online July 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761201Orig1s000lbl.pdf (Accessed January 13, 2022).

Newton, C. A., Adeel, S., Sadeghi-Yarandi, S., Powell, W., Migdal, A., Smiley, D., et al. (2013). Prevalence, Quality of Care, and Complications in Long Term Care Residents with Diabetes: a Multicenter Observational Study. *J. Am. Med. Dir. Assoc.* 14 (11), 842–846. doi:10.1016/j.jamda.2013.08.001

Resnick, H. E., Heineman, J., Stone, R., and Shorr, R. I. (2008). Diabetes in U.S. Nursing Homes, 2004. *Diabetes Care* 31 (2), 287–288. doi:10.2337/dc07-1425

Stern, A. D., Chen, J. L., Ouellet, M., Trusheim, M. R., El-Kilani, Z., Jessup, A., et al. (2021). Biosimilars and Follow-On Products In the United States: Adoption, Prices, and Users. *Health Aff.* 40 (6), 989–999. doi:10.1377/hlthaff.2020.02239

Tadrous, M., Shakeri, A., Hayes, K. N., Neville, H. L., Houlihan, J., Clement, F., et al. (2021). Canadian Trends and Projections in Prescription Drug Purchases: 2001-2023. *Can J. Health Technol.* 1 (11). doi:10.51731/cjht.2021.209

Tichy, E. M., Hoffman, J. M., Suda, K. J., Rim, M. H., Tadrous, M., Cuellar, S., et al. (2021). National Trends in Prescription Drug Expenditures and Projections for 2021. *Am. J. Health Syst. Pharm* 78 (14), 1294–1308. doi:10.1093/ajhp/zxab160

U.S. Food & Drug Administration (2021). Biologics License Application Approval: Insulin Glargine-Yfgn (Semglee). Published online July 28, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761201Orig1s000ltr.pdf (Accessed January 3, 2022).

U.S. Food & Drug Administration (2021). New Drug Application Approval: Insulin Glargine Injection (Semglee). Published online June 11, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/210605Orig1s000ltr.pdf (Accessed January 3, 2022).

U.S. Food & Drug Administration (2017). Prescribing Interchangeable Products. Published online October 23, 2017. Available at: https://www.fda.gov/media/108107/download (Accessed January 14, 2022).

U.S. Food & Drug Administration (2021). Purple Book Database of Licensed Biological Products. Published online December 30. Available at: https://purplebooksearch.fda.gov/(Accessed January 3, 2022).

White, E. M., Kosar, C. M., Feifer, R. A., Blackman, C., Gravenstein, S., Ouslander, J., et al. (2020). Variation in SARS-CoV-2 Prevalence in U.S. Skilled Nursing Facilities. *J. Am. Geriatr. Soc.* 68 (10), 2167–2173. doi:10.1111/jgs.16752

White, E. M., and Mor, V. (2021). SARS-CoV-2 Infection Among Nursing Home Residents. Reply. *N. Engl. J. Med.* 385 (20), e71. doi:10.1056/NEJMc2114113

White, E. M., Saade, E. A., Yang, X., Canaday, D. H., Blackman, C., Santostefano, C. M., et al. (2021). SARS-CoV-2 Antibody Detection in Skilled Nursing Facility Residents. *J. Am. Geriatr. Soc.* 69 (7), 1722–1728. doi:10.1111/jgs.17061

White, E. M., Yang, X., Blackman, C., Feifer, R. A., Gravenstein, S., and Mor, V. (2021). Incident SARS-CoV-2 Infection Among mRNA-Vaccinated and Unvaccinated Nursing Home Residents. *N. Engl. J. Med.* 385 (5), 474–476. doi:10.1056/NEJMc2104849

Zullo, A. R., Dore, D. D., Daiello, L., Baier, R. R., Gutman, R., Gifford, D. R., et al. (2016). National Trends in Treatment Initiation for Nursing Home Residents with Diabetes Mellitus, 2008 to 2010. *J. Am. Med. Dir. Assoc.* 17 (7), 602–608. doi:10.1016/j.jamda.2016.02.023

Zullo, A. R., Dore, D. D., Gutman, R., Mor, V., and Smith, R. J. (2016). National Glucose-Lowering Treatment Complexity Is Greater in Nursing Home Residents Than Community-Dwelling Adults. *J. Am. Geriatr. Soc.* 64 (11), e233–e235. doi:10.1111/jgs.14485

Conflict of Interest: KH has received grant funding from Genentech paid directly to Brown University for research related to influenza outbreak control in nursing homes. AZ has received grant funding from Sanofi Pasteur paid directly to Brown University for research on the epidemiology of infections and vaccines among older nursing home residents and infants.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 19 May 2022
doi: 10.3389/fphar.2022.879224

Second-Generation Long-Acting Injectable Antipsychotics and the Risk of Treatment Failure in a Population-Based Cohort

Donica Janzen[1], James M. Bolton[2], Christine Leong[1,2], I fan Kuo[1,3] and Silvia Alessi-Severini[1]*

[1]College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [2]Department of Psychiatry, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [3]Pharmaceutical, Laboratory and Blood Services Division, Ministry of Health, New Westminster, BC, Canada

Introduction: Second-generation long-acting injectable antipsychotics (SG-LAIAs) may improve outcomes compared to other antipsychotics. Real-world studies using linked administrative databases play an important role in assessing the comparative effectiveness of antipsychotic medications.

Methods: We used a prevalent new-user design in a population-based cohort of antipsychotic users with diagnosis of a psychotic disorder to compare the primary outcome of treatment failure, defined as psychiatric hospitalization, completed suicide, incarceration, or treatment discontinuation. Additional outcomes were all-cause mortality. SG-LAIA users were matched on a 1:1 basis with other antipsychotic users based on the time-conditional propensity score, calendar time, and prior antipsychotic exposure.

Results: The use of LAIAs was not associated with a lower risk of treatment failure than other antipsychotics (adjusted hazard ratio 1.07 and 95% confidence interval 0.98–1.15) but did reduce all-cause mortality (adjusted hazard ratio 0.69 and 95% confidence interval 0.48–0.99). Monotherapy with LAIAs was superior to other antipsychotic monotherapy (adjusted hazard ratio for treatment failure 0.83 and 95% confidence interval 0.78–0.89), and LAIAs were superior to other antipsychotics in antipsychotic-naïve users (adjusted hazard ratio for treatment failure 0.57 and 95% confidence interval 0.47–0.70).

Conclusion: In this population-based cohort, SG-LAIAs reduced the risk of treatment failure in incident new users but not in prevalent new users.

Keywords: antipsychotic treatment, long-acting injectable and oral antipsychotics, real-world data, comparative effectiveness, psychotic disorders

OPEN ACCESS

Edited by:
Andrea Burden,
ETH Zürich, Switzerland

Reviewed by:
Mary V. Seeman,
University of Toronto, Canada
Bo Ram Yang,
Chungnam National University, South Korea

****Correspondence:***
Donica Janzen
janzend6@myumanitoba.ca

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: *19 February 2022*
Accepted: *11 April 2022*
Published: *19 May 2022*

Citation:
Janzen D, Bolton JM, Leong C, Kuo If and Alessi-Severini S (2022) Second-Generation Long-Acting Injectable Antipsychotics and the Risk of Treatment Failure in a Population-Based Cohort. Front. Pharmacol. 13:879224. doi: 10.3389/fphar.2022.879224

INTRODUCTION

Long-acting injectable antipsychotics (LAIAs) have an established role for patients who require long-term antipsychotic treatment and are at risk of poor adherence; LAIAs improve adherence and persistence to antipsychotic treatment, which subsequently reduces the risk of relapse (Correll et al., 2016; Pilon et al., 2017; Greene et al., 2018). Clinical practice guidelines for the treatment of

schizophrenia recommend that all patients should be presented with LAIAs as a treatment option (Remington et al., 2017; American Psychiatric Association, 2021). The availability of long-acting injectable formulations of second-generation antipsychotics may improve patient acceptance of LAIAs, but their increased cost and formulary restrictions in some jurisdictions may be a barrier to the widespread use of second-generation long-acting injectable antipsychotics (Kane et al., 2019).

Observational study designs or pragmatic trials may be preferred over randomized controlled trials in studies of long-acting injectable antipsychotic effectiveness as they are more inclusive of patients with histories of non-adherence to treatment and multiple comorbidities (Alphs et al., 2014; Tiihonen et al., 2017). Randomized clinical trials have produced conflicting results, with some showing a reduced risk of relapse and treatment failure with LAIAs (Alphs et al., 2015; Subotnik et al., 2015), while others found no significant difference compared to oral antipsychotics (Kishimoto et al., 2014; Buckley et al., 2016). Improved clinical outcomes resulting from greater adherence to LAIAs may be obscured in controlled trials where adherence to assigned treatment is closely monitored (Correll et al., 2016). Observational studies also have limitations, most notably persistent confounding by unmeasured variables. Well-conducted observational studies can mitigate the risk of confounding with the incident user, active comparator designs, the use of propensity scores, and adjusting for measured covariates (Ray, 2003; Stürmer et al., 2014; Lund, Richardson and Sturmer, 2015). However, incident user designs limit sample size, particularly in the case of SG-LAIAs, where most new users have switched from an alternate antipsychotic. Prevalent new-user designs allow for the comparison of "switchers" to a newly marketed medication without restricting to treatment-naïve users (Suissa, Moodie and Dell'Aniello, 2017; Filion et al., 2020).

Many studies evaluate antipsychotic effectiveness in terms of treatment failure, treatment discontinuation, and hospitalization, but other outcomes may also be meaningful in this patient population. Population-based studies have established that patients with psychotic disorders are at increased risk of criminal justice system involvement (Khalifeh et al., 2015; Dean et al., 2018; Sariaslan et al., 2020). Antipsychotics may prevent reoffending in individuals with a history of incarceration (Fazel et al., 2014; Alphs et al., 2015; Chang et al., 2016; Rezansoff et al., 2017), but the literature on the role of antipsychotics in reducing crime in individuals without a history of justice system involvement is lacking. In the present study, we have used a prevalent new-user design in a population-based cohort of antipsychotic users to evaluate the risk of treatment failure, a composite endpoint of psychiatric hospitalization, completed suicide, incarceration, and treatment discontinuation, in SG-LAIA users versus oral antipsychotic users.

MATERIALS AND METHODS

Data Source

We used the Manitoba Population Research Data Repository, a collection of administrative health, education, social, justice, and registry databases, housed at the Manitoba Centre for Health Policy in Manitoba, Canada, to form a cohort of second-generation long-acting injectable antipsychotic (SG-LAIA) users (Suissa, Moodi,e and Dell'Aniello, 2017; Smith et al., 2018). The repository captures all prescriptions dispensed in the province of Manitoba, Canada, excluding in-hospital pharmaceuticals, and has been validated for SG-LAIAs (Janzen et al., 2022). We linked prescription claims to hospital discharge abstracts, medical service claims, prosecutions, vital statistics, and insurance registry data by a scrambled personal identification number. This study received ethics approval from the University of Manitoba Health Research Ethics Board under the project number HS20380 (H2016:468), the Manitoba Centre for Health Policy, the Health Information Privacy Committee, and Manitoba Justice.

Cohort Selection and Exposure Definition

We formed a base cohort of all individuals who were dispensed antipsychotic medication on the first date. An SG-LAIA was dispensed in Manitoba between 14 February 2005 and 31 March 2020 and had ≥ 1 year of continuous registration in the Manitoba Health Services Insurance Plan and ≥ 1 medical or hospital claim with a diagnosis of a psychotic disorder in the 3 years prior to cohort entry (Chartier et al., 2018). From the base cohort, we formed prevalent and incident new-user cohorts. Prevalent new users were defined as individuals who were dispensed an SG-LAIA and had a previous antipsychotic prescription in the 1 year prior to the SG-LAIA dispensation but no prior SG-LAIA in the 1-year look-back window. Incident new users were defined as individuals who were dispensed a new SG-LAIA with no prior antipsychotic dispensation in the previous year. For SG-LAIA new users, the cohort entry date (t_0) was defined as the date of the first dispensation. Subjects who received the oral equivalent of the incident SG-LAIA for less than 30 days before t_0 were included in the incident new-user cohort. For each SG-LAIA new user, we created an exposure set of eligible comparators who were dispensed antipsychotic medication within 120 days of t_0 and had the same prior duration of continuous antipsychotic use ± 180 days, prior year use of clozapine, prior year antipsychotic medications (0–1 or ≥ 2), and prior exposure to first-generation LAIA. For comparators, t_0 was defined as the dispensation date of any dispensation included in an exposure set. Subjects were excluded if the cohort exit date occurred on t_0. Additional subjects were excluded from the SG-LAIA new-user cohort if they had an incident antipsychotic dispensation other than an SG-LAIA on t_0 or if there were no eligible comparators in their exposure set.

The cohort members were included in a monotherapy subgroup if they were dispensed only one antipsychotic medication on t_0. Subjects in the monotherapy subgroup were censored upon the dispensation of an antipsychotic other than the incident antipsychotic.

Propensity Score Matching

Within each exposure set, we determined the propensity for initiation of SG-LAIAs at t_0. For comparators, a time-conditional propensity score was calculated at each

antipsychotic dispensation date in an exposure set. Covariates included in the propensity score were sex, age, income quintile, number of prior year medication classes dispensed, number of prior year hospitalizations, number of prior year physician visits, time since psychotic disorder diagnosis (defined as earliest of first antipsychotic dispensation or first hospitalization or medical claim with a diagnosis of psychotic disorder), prior year dispensation of psychotropic medication, psychiatric diagnoses in the previous 3 years, being accused of a crime in the previous 3 years, being a victim of a crime in the previous 3 years, and the calendar year of t_0. Exposure sets were excluded if the propensity score of the SG-LAIA new user was outside the range of propensity scores of comparators in the exposure set. SG-LAIA new users were matched on the basis of 1:1 with replacement with the comparator in the exposure set with the nearest time-conditional propensity score. Matching was performed in the chronological order, starting with the subject with the earliest t_0.

Outcome Definition

The cohort members were followed from t_0 to the occurrence of the outcome, death, emigration from Manitoba, or 31 March 2020. In addition, comparators were censored if they received SG-LAIA dispensation. The primary outcome was treatment failure, defined as psychiatric hospitalization (including hospitalization for a mood/anxiety disorder, substance use disorder, psychotic disorder, schizophrenia, or attempted suicide), incarceration, suicide (the primary cause of death being self-inflicted injury or poisoning or poisoning of undetermined intent), or treatment discontinuation (defined as a gap in prescription dispensations greater than 90 days). Additional outcomes included all-cause mortality and individual components of the composite primary outcome. We also conducted a subgroup analysis of prevalent and incident new users and restricted to subjects exposed to antipsychotic monotherapy only during the follow-up. Detailed definitions of outcomes are provided in **Supplementary Table S1**.

Statistical Analysis

We used descriptive statistics to evaluate cohort characteristics. We determined standardized differences to assess the covariate balance between exposure groups before and after matching. Outcomes were analyzed using a Cox proportional hazards regression model stratified by matched pair, adjusting for age, sex, time since psychotic disorder diagnosis, decile of the time-conditional propensity score, prior year hospital admissions, history of being accused of a crime, and diagnosis of personality disorder, substance use disorder, or mood/anxiety disorder. A robust sandwich variance estimate was included in the Cox model to account for matching with replacement. In addition, we used a modified Cox model to perform adjustments for the time-varying use of antipsychotic polypharmacy during the follow-up. All analyses were conducted in SAS® 9.4 (SAS Institute; Cary, NC).

Sensitivity Analysis

We repeated analyses in cohort members who had received a diagnosis of schizophrenia (ICD-9-CM code 295 or ICD-10-CA code F20) in the 3 years prior to t_0. We also conducted a *post hoc* sensitivity analysis including prior antipsychotics in the propensity score to evaluate the impact of baseline imbalance in prior antipsychotic medication.

RESULTS

Description of the Cohort

We identified 1,681 SG-LAIA new users and 14,225 antipsychotic user comparators eligible for matching. The final matched cohort included 1,182 matched pairs, with 187 in the incident new user cohort and 995 in the prevalent new-user cohort (**Figure 1**). The majority of SG-LAIA new users received risperidone-LAI (49.7%) on t0, followed by paliperidone-LAI (38.5%) and aripiprazole-LAI (11.8%). Among matched comparators, 86.9% received an oral SGA and 5.8% received an FG-LAIA on t0 (**Supplementary Table S2**). Baseline characteristics were well-balanced after matching, with standardized differences of less than 0.1 for all variables except for age groups less than 18 years and 18–30 years (**Table 1**, **Supplementary Table S3**). We adjusted Cox models for age to account for this imbalance.

The mean follow-up time for the primary outcome of treatment failure was 1.3 (SD 1.9) years for a total of 3,170 person years. In the SG-LAIA cohort, 913 experienced treatment failure in 1,512 person years of observation time for a crude incidence rate of 60.4 per 100 person years. Among matched comparators, there were 804 treatment failure events in 1,658 person years for a crude incidence rate of 48.5 per 100 person years. During 2,119 person years of observed monotherapy, there were 345 events in 653 person years of SG-LAIA monotherapy (crude incidence rate = 52.8 per 100 person years) and 704 events in 1,466 person years of monotherapy in the matched comparators (crude incidence rate = 48.0 per 100 person years). Baseline characteristics of the monotherapy subgroup are found in **Supplementary Tables S4, S5**.

Results of Cox Models

The SG-LAIA use was not associated with a reduced risk of treatment failure compared to the matched antipsychotic users (adjusted hazard ratio 1.07 and 95% confidence interval 0.98–1.15) (**Table 2**). However, the risk of treatment failure was reduced during SG-LAIA monotherapy compared to matched antipsychotic monotherapy (adjusted hazard ratio 0.83 and 95% confidence interval 0.78–0.89) (**Table 3**). The SG-LAIA use had no impact on the risk of incarceration (adjusted hazard ratio 0.97 and 95% confidence interval 0.76–1.25) or treatment discontinuation (adjusted hazard ratio 1.00 and 95% confidence interval 0.91–1.09) but increased the risk of psychiatric hospitalization (adjusted hazard ratio 1.38 and 95% confidence interval 1.23–1.54). A small number of suicides were observed during the follow-up, so results are not reported. In addition, the SG-LAIA use reduced the risk of all-cause mortality in the overall cohort (adjusted hazard ratio 0.69 and 95% confidence interval 0.48–0.99) and during monotherapy (adjusted hazard ratio 0.10 and 95% confidence interval 0.02–0.44).

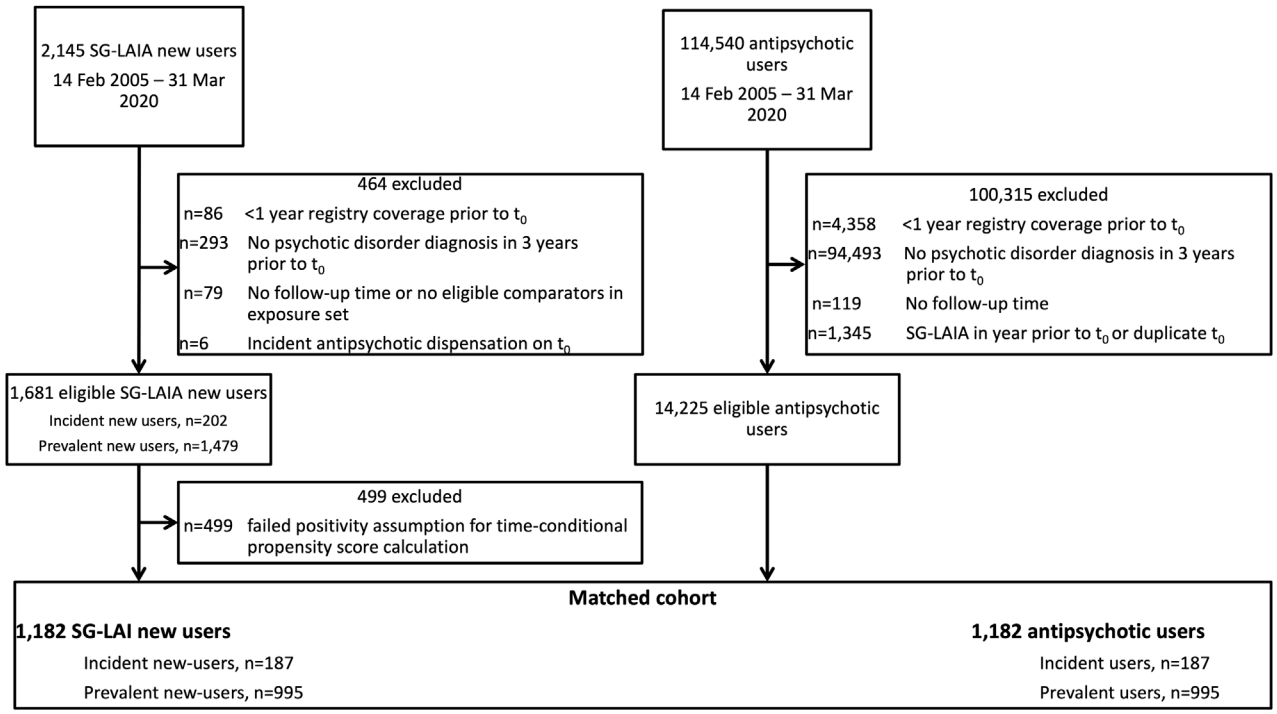


FIGURE 1 | Cohort selection.

Subgroups

Notable differences were observed in prevalent new users compared with incident new users (**Table 4**). Prevalent new users of SG-LAIAs had an increased risk of treatment failure (adjusted hazard ratio 1.20 and 95% confidence interval 1.01–1.32), psychiatric hospitalization (adjusted hazard ratio 1.50 and 95% confidence interval 1.31–1.71), and treatment discontinuation (adjusted hazard ratio 1.13 and 95% confidence interval 1.03–1.25). In contrast, a reduced risk of treatment failure (adjusted hazard ratio 0.57 and 95% confidence interval 0.47–0.70), incarceration (adjusted hazard ratio 0.32 and 95% confidence interval 0.11–0.99), and treatment discontinuation (adjusted hazard ratio 0.52 and 95% confidence interval 0.40–0.66) was observed in incident new users.

Sensitivity Analysis

Results in the cohort of SG-LAIA new users who had a diagnosis of schizophrenia were similar, with a few notable exceptions (**Supplementary Figures S1, S2**). There was no observed reduction in all-cause mortality (adjusted hazard ratio 0.79 and 95% hazard ratio 0.55–1.12), and there was a reduced risk of psychiatric hospitalization during monotherapy (adjusted hazard ratio 0.81 and 95% confidence interval 0.72–0.92). *Post hoc* sensitivity analysis where a prior antipsychotic was included in the time-conditional propensity score improved the baseline balance in the number of subjects previously treated with quetiapine and aripiprazole, with a minimal change in hazard ratios (**Supplementary Tables S6, S7**).

DISCUSSION

We used a prevalent new-user cohort design to evaluate the effectiveness of switching to an SG-LAIA compared with continuing an oral antipsychotic treatment regimen. In the overall cohort, we found the risk of treatment failure, incarceration, and treatment discontinuation was similar in SG-LAIA and oral antipsychotic users; the risk of psychiatric hospitalization was increased in SG-LAIA users, but the risk of all-cause mortality was decreased. Subsets of this population-based cohort benefitted from the SG-LAIA prescription, notably those receiving antipsychotic monotherapy and those who had no prior year of antipsychotic use, with the risk of treatment failure reduced by 17 and 43%, respectively. In contrast, prevalent antipsychotic users who switched to SG-LAIAs were found to have an increased risk of treatment failure, psychiatric hospitalization, and treatment discontinuation. Previous research has established that LAIAs have a greater benefit when used early in the course of the disease, but there is also evidence of effectiveness in prevalent antipsychotic users (Alphs et al., 2016; Tiihonen et al., 2017). Despite matching with the propensity score and a good balance of measured baseline variables including the duration of illness, prior antipsychotic exposure, and hospitalizations, we cannot rule out that this observation may be confounded. Patients switching to SG-LAIAs may not be comparable to those who were stabilized on a prior antipsychotic regimen. Crude hazard ratios shifted after adjusting for additional covariates, so the prevalent new-user design and propensity score matching were not sufficient to control confounding.

TABLE 1 | Baseline characteristics of cohort members before and after matching.

Characteristic	Before matching					After matching				
	SG-LAIA new users, *n* = 1,681		Antipsychotic users, *n* = 1,681[a]		Standardized difference	SG-LAIA new users, *n* = 1,182		Antipsychotic users, *n* = 1,182		Standardized difference
	n or mean	% or SD	n or mean	% or SD		n or mean	% or SD	n or mean	% or SD	
Females	604	35.9%	729	43.4%	0.15	435	36.8%	466	39.4%	0.05
Age (years)	36	16.3	50	21.0	0.72	37	17.2	37	17.4	0.00
Age group (years)										
<18	50	3.0%	70	4.2%	0.06	38	3.2%	111	9.4%	0.26
18–30	757	45.0%	314	18.7%	0.59	524	44.3%	424	35.9%	0.17
31–40	322	19.2%	221	13.1%	0.16	216	18.3%	237	20.1%	0.05
41–50	218	13.0%	279	16.6%	0.10	148	12.5%	178	15.1%	0.07
51–60	177	10.5%	300	17.8%	0.21	129	10.9%	120	10.2%	0.02
61–70	90	5.4%	198	11.8%	0.23	65	5.5%	51	4.3%	0.05
71–80	36	2.1%	113	6.7%	0.22	34	2.9%	23	1.9%	0.06
>80	31	1.8%	186	11.1%	0.38	28	2.4%	38	3.2%	0.05
Income quintile										
1 (lowest)	622	37.0%	597	35.5%	0.03	449	38.0%	457	38.7%	0.01
2	346	20.6%	369	22.0%	0.03	252	21.3%	241	20.4%	0.02
3	214	12.7%	232	13.8%	0.03	152	12.9%	143	12.1%	0.02
4	192	11.4%	169	10.1%	0.04	140	11.8%	145	12.3%	0.01
5 (highest)	127	7.6%	163	9.7%	0.08	93	7.9%	109	9.2%	0.05
Missing	180	10.7%	151	9.0%	0.06	96	8.1%	87	7.4%	0.03
Year of cohort entry										
2005/2006	45	2.7%	49	2.9%	0.01	41	3.5%	40	3.4%	0.00
2007/2008	81	4.8%	74	4.4%	0.02	60	5.1%	61	5.2%	0.00
2009/2010	105	6.2%	111	6.6%	0.01	74	6.3%	74	6.3%	0.00
2011/2012	183	10.9%	183	10.9%	0.00	124	10.5%	129	10.9%	0.01
2013/2014	196	11.7%	196	11.7%	0.00	129	10.9%	122	10.3%	0.02
2015/2016	363	21.6%	360	21.4%	0.00	246	20.8%	243	20.6%	0.01
2017/2018	413	24.6%	414	24.6%	0.00	288	24.4%	298	25.2%	0.03
2019/2020	295	17.5%	294	17.5%	0.00	224	19.0%	215	18.2%	0.02
Time since psychotic disorder diagnosis (years)	8.1	6.7	10.1	7.8	0.28	7.2	6.7	7.2	6.6	0.00
<1	237	14.1%	237	14.1%	0.00	229	19.4%	228	19.3%	0.00
1–4.9	499	29.7%	401	23.9%	0.13	375	31.7%	368	31.1%	0.01
5–10	341	20.3%	229	13.6%	0.18	197	16.7%	209	17.7%	0.03
>10	604	35.9%	814	48.4%	0.26	381	32.2%	377	31.9%	0.01
Prior FG-LAIA use	389	23.1%	389	23.1%	0.00	152	12.9%	152	12.9%	0.00
Prior year antipsychotic medications										
0–1	799	47.5%	799	47.5%	0.00	701	59.3%	701	59.3%	0.00
>1	749	44.6%	749	44.6%	0.00	407	34.4%	407	34.4%	0.00
Clozapine	133	7.9%	133	7.9%	0.00	74	6.3%	74	6.3%	0.00
Prior year number of medication classes dispensed										
0–1	454	27.0%	243	14.5%	0.31	338	28.6%	319	27.0%	0.04
2–5	604	35.9%	533	31.7%	0.09	432	36.5%	430	36.4%	0.00
>5	623	37.1%	905	53.8%	0.34	412	34.9%	433	36.6%	0.04
Prior year medication use										
Mood stabilizer	280	16.7%	309	18.4%	0.05	188	15.9%	169	14.3%	0.04
Antidepressant	595	35.4%	795	47.3%	0.24	414	35.0%	452	38.2%	0.07
Anxiolytic	612	36.4%	701	41.7%	0.11	403	34.1%	410	34.7%	0.01
Sedative-hypnotic	320	19.0%	412	24.5%	0.13	227	19.2%	225	19.0%	0.00
Anticonvulsant	94	5.6%	172	10.2%	0.17	70	5.9%	62	5.2%	0.03
Psychostimulant	51	3.0%	16	1.0%	0.15	33	2.8%	39	3.3%	0.03
Anticholinergic	397	23.6%	332	19.8%	0.09	233	19.7%	224	19.0%	0.02
Opioid	324	19.3%	371	22.1%	0.07	220	18.6%	222	18.8%	0.00
Opioid agonist therapy	13	2.2%	S	S	0.07	8	0.7%	14	1.2%	0.05
Smoking cessation aid	64	3.8%	68	4.0%	0.01	44	3.7%	41	3.5%	0.01
Alcohol use disorder drug	11	0.7%	S	S	0.06	S	S	S	S	0.03
Dementia drug	6	0.4%	65	3.9%	0.25	S	S	S	S	0.01
Antidiabetic drug	165	9.8%	278	16.5%	0.20	103	8.7%	108	9.1%	0.01
Antihyperlipidemic drug	130	7.7%	300	17.8%	0.31	86	7.3%	93	7.9%	0.02
Comorbidities										
Mood or anxiety disorder	1,283	76.3%	1,373	81.7%	0.13	906	76.6%	916	77.5%	0.02

(Continued on following page)

TABLE 1 | (*Continued*) Baseline characteristics of cohort members before and after matching.

Characteristic	Before matching					After matching				
	SG-LAIA new users, *n* = 1,681		Antipsychotic users, *n* = 1,681[a]		Standardized difference	SG-LAIA new users, *n* = 1,182		Antipsychotic users, *n* = 1,182		Standardized difference
	n or mean	% or SD	n or mean	% or SD		n or mean	% or SD	n or mean	% or SD	
Personality disorder	485	28.9%	472	28.1%	0.02	308	26.1%	308	26.1%	0.00
Substance use disorder	967	57.5%	726	43.2%	0.29	638	54.0%	632	53.5%	0.01
Dementia	201	12.0%	439	26.1%	0.37	146	12.4%	159	13.5%	0.03
Autism spectrum disorder	40	2.4%	41	2.4%	0.00	30	2.5%	29	2.5%	0.01
Intellectual disability/ developmental disorder	199	11.8%	138	8.2%	0.12	117	9.9%	116	9.8%	0.00
ADHD	241	14.3%	120	7.1%	0.23	149	12.6%	171	14.5%	0.05
Suicide attempt	184	10.9%	144	8.6%	0.08	107	9.1%	120	10.2%	0.04
Prior year hospitalizations										
0	474	28.2%	1,064	63.3%	0.75	393	33.2%	391	33.1%	0.00
1–2	973	57.9%	550	32.7%	0.52	687	58.1%	690	58.4%	0.01
>2	234	13.9%	67	4.0%	0.35	102	8.6%	101	8.5%	0.00
Prior year physician visits										
0–2	61	3.6%	109	6.5%	0.13	54	4.6%	64	5.4%	0.04
3–5	127	7.6%	154	9.2%	0.06	97	8.2%	89	7.5%	0.03
>5	1,493	88.8%	1,418	84.4%	0.13	1,031	87.2%	1,029	87.1%	0.01
Incidents where accused of a crime										
0	1,156	68.8%	1,485	88.3%	0.49	851	72.0%	877	74.2%	0.05
1–2	232	13.8%	113	6.7%	0.23	153	12.9%	151	12.8%	0.01
>2	293	17.4%	83	4.9%	0.40	178	15.1%	154	13.0%	0.06
Incidents where victim of a crime										
0	1,585	94.3%	1,630	97.0%	0.13	1,129	95.5%	1,124	95.1%	0.02
>0	96	5.7%	51	3.0%	0.13	53	4.5%	58	4.9%	0.02

[a]*Cohort before matching consisted of SG-LAIA new users and antipsychotic users in the exposure set of an SG-LAIA new-user design. Exposure sets were based on calendar time, prior duration of continuous antipsychotic use, prior year use of clozapine, prior use of FG-LAIA, and prior year number of unique antipsychotic medication dispensed. Characteristics of a random sample of one antipsychotic user per exposure set are reported. SG-LAIA users were matched on the basis of 1:1 with an antipsychotic user on the time-conditional propensity score.*
ADHD = attention-deficit hyperactivity disorder; FGA = first-generation antipsychotic; FG-LAIA = first-generation long-acting injectable antipsychotic; LAI = long-acting injectable; S = suppressed due to count < 6; SD = standard deviation; SGA = second-generation antipsychotic; SG-LAIA = second-generation long-acting injectable antipsychotic.

TABLE 2 | Association between second-generation long-acting injectable antipsychotics versus oral antipsychotics and treatment failure, psychiatric hospitalization, incarceration, treatment discontinuation and all-cause mortality.

	Number of events	Person years	Crude incidence rate per 100 person years	Crude hazard ratio (95% CI)		Adjusted hazard ratio[a] (95% CI)	
Treatment failure							
SG-LAIA new users	913	1,512	60.4	1.14	(1.10–1.17)	1.07	(0.98–1.15)
Matched antipsychotic users	804	1,658	48.5	1.00	(Reference)	1.00	(Reference)
Psychiatric hospitalization							
SG-LAIA new users	568	2,844	20.0	1.17	(1.11–1.25)	1.38	(1.23–1.54)
Matched antipsychotic users	484	2,979	16.2	1.00	(Reference)	1.00	(Reference)
Incarceration							
SG-LAIA new users	172	4,409	3.9	1.11	(0.97–1.27)	0.97	(0.76–1.25)
Matched antipsychotic users	155	3,965	3.9	1.00	(Reference)	1.00	(Reference)
Treatment discontinuation							
SG-LAIA new users	808	2,139	37.8	1.22	(1.17–1.27)	1.00	(0.91–1.09)
Matched antipsychotic users	663	2,157	30.7	1.00	(Reference)	1.00	(Reference)
All-cause mortality							
SG-LAIA new users	91	5,198	1.8	1.06	(0.88–1.27)	0.69	(0.48–0.99)
Matched antipsychotic users	86	4,552	1.9	1.00	(Reference)	1.00	(Reference)

[a]*Adjusted for time-varying use of additional antipsychotic medication in each 3-month period of follow-up time and baseline variables that include age, sex, time since psychotic disorder diagnosis, decile of time-conditional propensity score, prior year hospital admissions, being accused of a crime, diagnosis of personality disorder, substance use disorder, and mood/anxiety disorder.*
SG-LAIA, second-generation long-acting injectable antipsychotic.

TABLE 3 | Association between second-generation long-acting injectable antipsychotic monotherapy versus oral antipsychotic monotherapy and treatment failure, psychiatric hospitalization, incarceration, treatment discontinuation, and all-cause mortality.

	Number of events	Person years	Crude incidence rate per 100 person years	Crude hazard ratio (95% CI)		Adjusted hazard ratio[a] (95% CI)	
Treatment failure							
SG-LAIA new users	345	653	52.8	0.84	(0.79–0.90)	0.83	(0.78–0.89)
Matched antipsychotic users	704	1,466	48.0	1.00	(Reference)	1.00	(Reference)
Psychiatric hospitalization							
SG-LAIA new users	209	964	21.7	1.01	(0.86–1.18)	1.03	(0.86–1.24)
Matched antipsychotic users	373	2,215	16.8	1.00	(Reference)	1.00	(Reference)
Incarceration							
SG-LAIA new users	77	1,209	6.4	0.86	(0.67–1.10)	0.68	(0.43–1.09)
Matched antipsychotic users	125	2,797	4.5	1.00	(Reference)	1.00	(Reference)
Treatment discontinuation							
SG-LAIA new users	223	817	27.3	0.70	(0.60–0.82)	0.67	(0.57–0.79)
Matched antipsychotic users	485	1,697	28.6	1.00	(Reference)	1.00	(Reference)
All-cause mortality							
SG-LAIA new users	21	1,386	1.5	0.55	(0.34–0.86)	0.10	(0.02–0.44)
Matched antipsychotic users	63	3,312	1.9	1.00	(Reference)	1.00	(Reference)

[a]*Adjusted for baseline variables age, sex, time since psychotic disorder diagnosis, decile of time-conditional propensity score, prior year hospital admissions, being accused of a crime, diagnosis of personality disorder, substance use disorder, and mood/anxiety disorder.*
SG-LAIA, second-generation long-acting injectable antipsychotic.

TABLE 4 | Association between second-generation long-acting injectable antipsychotics versus oral antipsychotics and treatment failure, psychiatric hospitalization, incarceration, treatment discontinuation, and all-cause mortality in prevalent and incident new users.

	Number of events	Person years	Crude incidence rate per 100 person years	Crude hazard ratio (95% CI)		Adjusted hazard ratio[a] (95% CI)	
Treatment failure							
SG-LAIA prevalent new users	771	1,276	60.4	1.19	(1.15–1.23)	1.20	(1.10–1.32)
Matched antipsychotic prevalent users	648	1,541	42.1	1.00	(Reference)	1.00	(Reference)
SG-LAIA incident new users	142	236	60.2	0.91	(0.85–0.98)	0.57	(0.47–0.70)
Matched antipsychotic incident users	156	117	133.3	1.00	(Reference)	1.00	(Reference)
Psychiatric hospitalization							
SG-LAIA prevalent new users	480	2,384	20.1	1.19	(1.11–1.26)	1.50	(1.31–1.71)
Matched Antipsychotic prevalent Users	405	2,577	15.7	1.00	(Reference)	1.00	(Reference)
SG-LAIA incident new users	88	459	19.2	1.11	(0.96–1.29)	1.06	(0.81–1.30)
Matched antipsychotic incident users	79	402	19.7	1.00	(Reference)	1.00	(Reference)
Incarceration							
SG-LAIA prevalent new users	147	3,744	3.9	1.24	(1.06–1.44)	1.10	(0.85–1.43)
Matched antipsychotic prevalent users	119	3,425	3.5	1.00	(Reference)	1.00	(Reference)
SG-LAIA incident new users	25	665	3.8	0.69	(0.50–0.97)	0.32	(0.11–0.99)
Matched antipsychotic incident users	36	540	6.7	1.00	(Reference)	1.00	(Reference)
Treatment discontinuation							
SG-LAIA prevalent new users	685	1,829	37.5	1.31	(1.25–1.37)	1.13	(1.03–1.25)
Matched antipsychotic prevalent users	525	1,976	26.6	1.00	(Reference)	1.00	(Reference)
SG-LAIA incident new users	123	310	39.7	0.89	(0.81–0.98)	0.52	(0.40–0.66)
Matched antipsychotic incident users	138	181	76.2	1.00	(Reference)	1.00	(Reference)

[a]*Adjusted for the time-varying use of additional antipsychotic medications in each 3-month period of follow-up time, and baseline variables such as age, sex, time since psychotic disorder diagnosis, decile of the time-conditional propensity score, prior year hospital admissions, being accused of a crime, diagnosis of personality disorder, substance use disorder, and mood/anxiety disorder.*
SG-LAIA, second-generation long-acting injectable antipsychotic.

Other observational studies have found that the SG-LAIA use reduces the risk of treatment failure, treatment discontinuation, hospitalization, and mortality compared with oral antipsychotics (Tiihonen et al., 2011, 2017; Stip and Lachaine, 2018; Taipale et al., 2018; Song et al., 2019). Tiihonen et al. observed adjusted hazard ratios for the risk of treatment failure during monotherapy with paliperidone-LAI and risperidone-LAI of 0.80 and 0.72, respectively, compared with oral olanzapine monotherapy in a Swedish population-based cohort (Tiihonen et al., 2017). Taipale et al. also demonstrated an increased risk of mortality with oral antipsychotics and FG-LAIAs compared to SG-LAIAs in the same Swedish cohort (adjusted hazard ratio 1.51 for oral SGAs, 1.83 for oral FGAs, and 1.37 for FG-LAIAs) (Taipale et al., 2018). Despite the demonstrated benefits of LAIA treatment, event rates were considerable. Our study estimated crude incidence rates of approximately 60 treatment failure events, 25 psychiatric hospitalizations, and 38 treatment discontinuation events per 100 person years of SG-LAIA exposure. Similar or higher rates were observed in the Swedish cohort for treatment failure (IR 9.3 and 6.4 per 10 person years for paliperidone- and risperidone-LAI, respectively) and psychiatric hospitalization (IR 5.1 and 3.8 per 10 person years for paliperidone and risperidone LAI, respectively) (Tiihonen et al., 2017).

We observed a non-significant trend toward reduction in the risk of incarceration in the overall cohort and a remarkable 68% reduction in the risk of incarceration in incident new users of SG-LAIA. This finding is in line with previous research, including a pragmatic randomized trial that showed paliperidone-LAI reduced time to incarceration (Alphs et al., 2015) and a cohort study showing a 70% reduction in the risk of violent crimes during LAIA treatment (Fazel et al., 2014).

While observational designs of SG-LAIA effectiveness can be subject to unmeasured confounding, the direction of bias in this study is most likely in favor of an active comparator for a few reasons. First, LAIA users have been shown to have more severe diseases than patients who were not prescribed LAIAs (Kishimoto et al., 2018). Second, in Manitoba, SG-LAIA agents are reserved as second-line agents, for patients with evidence of non-adherence, treatment failure, or intolerance to another antipsychotic. Third, the increased frequency of contact between SG-LAIA users and healthcare providers introduces detection bias, as the need for hospitalization or treatment escalation is detected earlier in patients who are monitored more frequently. Thus, we are more confident in our results that show significant reductions in the risk of outcomes associated with SG-LAIA use than we are in those that show an increased risk.

This study has numerous strengths. By using a prevalent new-user design, we were able to increase our sample size by almost 1,000 patients. The data used from the Manitoba Population Research Data Repository have undergone a rigorous quality assessment, and we used established definitions to identify comorbidities and outcomes (Chartier et al., 2018; Smith et al., 2018). We had a 20-year study period with over 3,100 person years of observation time. We included incarceration as a reason for treatment failure and adjusted for having been accused of a crime. Finally, we have previously validated SG-LAIA exposure in prescription claim data (Janzen et al., 2022).

This study reinforces the evidence from previous work, suggesting LAIAs are superior to oral antipsychotics at the early stages of the disease and during monotherapy. We encourage clinicians to offer SG-LAIA treatment to all patients initiating antipsychotic therapy. However, it remains unclear whether there is a benefit to switching stable patients from oral antipsychotics to SG-LAIAs.

CONCLUSION

In this population-based cohort study, the SG-LAIA use was not associated with a reduced risk of treatment failure compared with other antipsychotics but did reduce mortality. Monotherapy with SG-LAIAs and the incident use of SG-LAIAs were associated with a reduced risk of treatment failure.

DATA AVAILABILITY STATEMENT

The data analyzed in this study are subject to the following licenses/restrictions. Data used in this article were derived from administrative health and social data as a secondary use. The data were provided under specific data sharing agreements only for approved use at the Manitoba Centre for Health Policy (MCHP). The original source data are not owned by the researchers or MCHP and as such cannot be provided to a public repository. The original data source and approval for use have been noted in the acknowledgments of the article. If necessary, source data specific to this article or project may be reviewed at MCHP with the consent of the original data providers, along with the required privacy and ethical review bodies. Requests to access these datasets should be directed to the Manitoba Centre for Health Policy, https://umanitoba.ca/manitoba-centre-for-health-policy/data-repository.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Manitoba Health Research Ethics Board (project number HS20380/H2016:468). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study, in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DJ designed the study, conducted the literature review, analyzed the data, and wrote the first draft of the manuscript. CL and JB contributed to the study design and provided clinical expertise. IK and SA-S supervised all phases of the project. All authors contributed to and approved the final version of the manuscript.

FUNDING

This project was supported by the Evelyn Shapiro Award for Health Services Research to DJ, the Leslie F. Buggey Professorship in Pharmacy to SA-S and the University of Manitoba.

ACKNOWLEDGMENTS

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project #2017-016 (HIPC#2016/2017-64). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health, Manitoba Vital Statistics and Manitoba Justice.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.879224/full#supplementary-material

REFERENCES

Alphs, L., Benson, C., Cheshire-Kinney, K., Lindenmayer, J. P., Mao, L., Rodriguez, S. C., et al. (2015). Real-world Outcomes of Paliperidone Palmitate Compared to Daily Oral Antipsychotic Therapy in Schizophrenia: A Randomized, Open-Label, Review Board-Blinded 15-month Study. *J. Clin. Psychiatry* 76 (5), 554–561. doi:10.4088/JCP.14m09584

Alphs, L., Mao, L., Rodriguez, S. C., Hulihan, J., and Starr, H. L. (2014). Design and Rationale of the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) Study: A Novel Comparative Trial of Once-Monthly Paliperidone Palmitate versus Daily Oral Antipsychotic Treatment for Delaying Time to Treatment Failure in Persons with Schizophrenia. *J. Clin. Psychiatry* 75 (12), 1388–1393. doi:10.4088/JCP.13m08965

Alphs, L., Nasrallah, H. A., Bossie, C. A., Fu, D. J., Gopal, S., Hough, D., et al. (2016). Factors Associated with Relapse in Schizophrenia Despite Adherence to Long-Acting Injectable Antipsychotic Therapy. *Int. Clin. Psychopharmacol.* 31 (4), 202–209. doi:10.1097/YIC.0000000000000125

American Psychiatric Association (2021). *Practice Guideline for the Treatment of Patients with Schizophrenia*. 3rd edn.. Washington, DC: American Psychiatric Association

Buckley, P. F., Schooler, N. R., Goff, D. C., Kopelowicz, A., Lauriello, J., Manschreck, T. C., et al. (2016). Comparison of Injectable and Oral Antipsychotics in Relapse Rates in a Pragmatic 30-month Schizophrenia Relapse Prevention Study. *Psychiatr. Serv.* 67 (12), 1370–1372. doi:10.1176/appi.ps.201500466

Chang, Z., Lichtenstein, P., Långström, N., Larsson, H., and Fazel, S. (2016). Association between Prescription of Major Psychotropic Medications and Violent Reoffending after Prison Release. *JAMA* 316 (17), 1798–1807. doi:10.1001/jama.2016.15380

Chartier, M., Bolton, J. M., Mota, N., MacWilliam, L., Ekuma, O., Nie, Y., et al. (2018). *Mental Illness Among Adult Manitobans*. Winnipeg, MB: Manitoba Centre for Health Policy

Correll, C. U., Citrome, L., Haddad, P. M., Lauriello, J., Olfson, M., Calloway, S. M., et al. (2016). The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence. *J. Clin. Psychiatry* 77 (Suppl. 3), 1–24. doi:10.4088/jcp.15032su1

Dean, K., Laursen, T. M., Pedersen, C. B., Webb, R. T., Mortensen, P. B., and Agerbo, E. (2018). Risk of Being Subjected to Crime, Including Violent Crime, after Onset of Mental Illness: A Danish National Registry Study Using Police Data. *JAMA Psychiatry* 75 (7), 689–696. doi:10.1001/jamapsychiatry.2018.0534

Fazel, S., Zetterqvist, J., Larsson, H., Långström, N., and Lichtenstein, P. (2014). Antipsychotics, Mood Stabilisers, and Risk of Violent Crime. *Lancet* 384 (9949), 1206–1214. doi:10.1016/S0140-6736(14)60379-2

Filion, K. B., Lix, L. M., Yu, O. H., Dell'Aniello, S., Douros, A., Shah, B. R., et al. (2020). Sodium Glucose Cotransporter 2 Inhibitors and Risk of Major Adverse Cardiovascular Events: Multi-Database Retrospective Cohort Study. *BMJ* 370, m3342. doi:10.1136/bmj.m3342

Greene, M., Yan, T., Chang, E., Hartry, A., Touya, M., and Broder, M. S. (2018). Medication Adherence and Discontinuation of Long-Acting Injectable versus Oral Antipsychotics in Patients with Schizophrenia or Bipolar Disorder. *J. Med. Econ.* 21 (2), 127–134. doi:10.1080/13696998.2017.1379412

Janzen, D., Bolton, J. M., Leong, C., Kuo, I., Alessi-Severini, S., et al. (2022). Long-acting Injectable Antipsychotics in a Prescription Claims Data Source: a Validation Study. *Drugs - Real World Outcomes*.

Kane, J. M., Schooler, N. R., Marcy, P., Achtyes, E. D., Correll, C. U., Robinson, D. G., et al. (2019). Patients with Early-phase Schizophrenia Will Accept Treatment with Sustained-Release Medication (Long-acting Injectable Antipsychotics): Results from the Recruitment Phase of the PRELAPSE Trial. *J. Clin. Psychiatry* 80 (3), 22–18m12546. doi:10.4088/jcp.18m12546

Khalifeh, H., Johnson, S., Howard, L. M., Borschmann, R., Osborn, D., Dean, K., et al. (2015). Violent and Non-violent Crime against Adults with Severe Mental Illness. *Br. J. Psychiatry* 206 (4), 275–282. doi:10.1192/bjp.bp.114.147843

Kishimoto, T., Hagi, K., Nitta, M., Leucht, S., Olfson, M., Kane, J. M., et al. (2018). Effectiveness of Long-Acting Injectable vs Oral Antipsychotics in Patients with Schizophrenia: A Meta-Analysis of Prospective and Retrospective Cohort Studies. *Schizophr Bull.* 44 (3), 603–619. doi:10.1093/schbul/sbx090

Kishimoto, T., Robenzadeh, A., Leucht, C., Leucht, S., Watanabe, K., Mimura, M., et al. (2014). Long-acting Injectable vs Oral Antipsychotics for Relapse Prevention in Schizophrenia: a Meta-Analysis of Randomized Trials. *Schizophr Bull.* 40 (1), 192–213. doi:10.1093/schbul/sbs150

Lund, J. L., Richardson, D. B., and Stürmer, T. (2015). The Active Comparator, New User Study Design in Pharmacoepidemiology: Historical Foundations and Contemporary Application. *Curr. Epidemiol. Rep.* 2 (4), 221–228. doi:10.1007/s40471-015-0053-5

Pilon, D., Tandon, N., Lafeuille, M. H., Kamstra, R., Emond, B., Lefebvre, P., et al. (2017). Treatment Patterns, Health Care Resource Utilization, and Spending in Medicaid Beneficiaries Initiating Second-Generation Long-Acting Injectable Agents versus Oral Atypical Antipsychotics. *Clin. Ther.* 39 (10), 1972–e2. doi:10.1016/j.clinthera.2017.08.008

Ray, W. A. (2003). Evaluating Medication Effects outside of Clinical Trials: New-User Designs. *Am. J. Epidemiol.* 158 (9), 915–920. doi:10.1093/aje/kwg231

Remington, G., Addington, D., Honer, W., Ismail, Z., Raedler, T., and Teehan, M. (2017). Guidelines for the Pharmacotherapy of Schizophrenia in Adults. *Can. J. Psychiatry* 62 (9), 604–616. doi:10.1177/0706743717720448

Rezansoff, S. N., Moniruzzaman, A., Fazel, S., McCandless, L., and Somers, J. M. (2017). Adherence to Antipsychotic Medication and Criminal Recidivism in a Canadian Provincial Offender Population. *Schizophr Bull.* 43 (5), 1002–1010. doi:10.1093/schbul/sbx084

Sariaslan, A., Arseneault, L., Larsson, H., Lichtenstein, P., and Fazel, S. (2020). Risk of Subjection to Violence and Perpetration of Violence in Persons with Psychiatric Disorders in Sweden. *JAMA Psychiatry* 77 (4), 359–367. doi:10.1001/jamapsychiatry.2019.4275

Smith, M., Lix, L. M., Azimaee, M., Enns, J. E., Orr, J., Hong, S., et al. (2018). Assessing the Quality of Administrative Data for Research: A Framework from

the Manitoba Centre for Health Policy. *J. Am. Med. Inform. Assoc.* 25 (3), 224–229. doi:10.1093/jamia/ocx078

Song, X., El Khoury, A. C., Brouillette, M., Smith, D., and Joshi, K. (2019). Treatment Discontinuation of Long-Acting Injectables or Oral Atypical Antipsychotics Among Medicaid Recipients with Schizophrenia. *J. Med. Econ.* 22 (11), 1105–1112. doi:10.1080/13696998.2019.1615927

Stip, E., and Lachaine, J. (2018). Real-world Effectiveness of Long-Acting Antipsychotic Treatments in a Nationwide Cohort of 3957 Patients with Schizophrenia, Schizoaffective Disorder and Other Diagnoses in Quebec. *Ther. Adv. Psychopharmacol.* 8 (11), 287–301. doi:10.1177/2045125318782694

Stürmer, T., Wyss, R., Glynn, R. J., and Brookhart, M. A. (2014). Propensity Scores for Confounder Adjustment when Assessing the Effects of Medical Interventions Using Nonexperimental Study Designs. *J. Intern. Med.* 275 (6), 570–580. doi:10.1111/joim.12197

Subotnik, K. L., Casaus, L. R., Ventura, J., Luo, J. S., Hellemann, G. S., Gretchen-Doorly, D., et al. (2015). Long-Acting Injectable Risperidone for Relapse Prevention and Control of Breakthrough Symptoms after a Recent First Episode of Schizophrenia. A Randomized Clinical Trial. *JAMA Psychiatry* 72 (8), 822–829. doi:10.1001/jamapsychiatry.2015.0270

Suissa, S., Moodie, E. E., and Dell'Aniello, S. (2017). Prevalent New-User Cohort Designs for Comparative Drug Effect Studies by Time-Conditional Propensity Scores. *Pharmacoepidemiol. Drug Saf.* 26 (4), 459–468. doi:10.1002/pds.4107

Taipale, H., Mittendorfer-Rutz, E., Alexanderson, K., Majak, M., Mehtälä, J., Hoti, F., et al. (2018). Antipsychotics and Mortality in a Nationwide Cohort of 29,823 Patients with Schizophrenia. *Schizophrenia Res.* 197, 274–280. doi:10.1016/j.schres.2017.12.010

Tiihonen, J., Haukka, J., Taylor, M., Haddad, P. M., Patel, M. X., and Korhonen, P. (2011). A Nationwide Cohort Study of Oral and Depot Antipsychotics after First Hospitalization for Schizophrenia. *Am. J. Psychiatry* 168 (6), 603–609. doi:10.1176/appi.ajp.2011.10081224

Tiihonen, J., Mittendorfer-Rutz, E., Majak, M., Mehtälä, J., Hoti, F., Jedenius, E., et al. (2017). Real-world Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients with Schizophrenia. *JAMA Psychiatry* 74 (7), 686–693. doi:10.1001/jamapsychiatry.2017.1322

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 30 May 2022
doi: 10.3389/fphar.2022.871052

Time to Treatment Intensification in Patients Receiving DPP4 Inhibitors *Versus* Sulfonylureas as the First Add-On to Metformin Monotherapy: A Retrospective Cohort Study

Giuseppe Roberto[1], Anna Girardi[1], Francesco Barone-Adesi[2], Alessandro Pecere[2], Valentina Ientile[3], Claudia Bartolini[1], Roberto Da Cas[4], Stefania Spila-Alegiani[4], Carmen Ferrajolo[5], Paolo Francesconi[1], Gianluca Trifirò[3], Elisabetta Poluzzi[6], Fabio Baccetti[7] and Rosa Gini[1]*

[1]Osservatorio di Epidemiologia, Agenzia Regionale di Sanità Della Toscana, Firenze, Italy, [2]Dipartimento di Medicina Traslazionale, Università Del Piemonte Orientale, Novara, Italy, [3]Dipartimento di Scienze Biomediche, Odontoiatriche e Delle Immagini Morfologiche e Funzionali, Università Degli Studi di Messina, Messina, Italy, [4]Centro Nazionale per la Ricerca e la Valutazione Preclinica e Clinica Dei Farmaci, Istituto Superiore di Sanità, Roma, Italy, [5]Dipartimento di Medicina Sperimentale, Università Degli Studi Della Campania "L. Vanvitelli" e Centro Regionale di Farmacovigilanza, Regione Campania, Napoli, Italy, [6]Unità di Farmacologia, Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy, [7]Unità Operativa di Diabetologia Massa-Carrara, USL Toscana Nordovest, Massa, Italy

OPEN ACCESS

Edited by:
Andrea Burden,
ETH Zürich, Switzerland

Reviewed by:
Judith De Ruijter–Van Dalem,
Maastricht University Medical Centre, Netherlands
Diogo Mendes,
University of Coimbra, Portugal

***Correspondence:**
Giuseppe Roberto
giuseppe.roberto@ars.toscana.it

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: 07 February 2022
Accepted: 11 April 2022
Published: 30 May 2022

Citation:
Roberto G, Girardi A, Barone-Adesi F, Pecere A, Ientile V, Bartolini C, Da Cas R, Spila-Alegiani S, Ferrajolo C, Francesconi P, Trifirò G, Poluzzi E, Baccetti F and Gini R (2022) Time to Treatment Intensification in Patients Receiving DPP4 Inhibitors Versus Sulfonylureas as the First Add-On to Metformin Monotherapy: A Retrospective Cohort Study. Front. Pharmacol. 13:871052. doi: 10.3389/fphar.2022.871052

Background: To verify whether, in patients on metformin (MET) monotherapy for type 2 diabetes (T2D), the add-on of a dipeptidyl peptidase inhibitor (DPP4i) compared to a sulfonylurea (SU) can delay the time to the subsequent treatment intensification (TI).

Methods: Population-based administrative data banks from four Italian geographic areas were used. Patients aged ≥18 years on MET monotherapy receiving first DPP4i or SU dispensing between 2008 and 2015 (cohort entry) were followed up to the occurrence of TI (insulin dispensing or add-on of a third non-insulin hypoglicemic >180 days after cohort entry), treatment discontinuation, switch, cancer, death, TI occurrence within, end of data availability, end of study period (31 December 2016), whichever came first. Patients on MET + DPP4i were matched 1:1 with those on MET + SU by sex, age, year of cohort entry, and data bank. Hazard Ratio (HR) and 95% confidence intervals (95%CI) were estimated using multivariable Cox regression model including matching variables and potential confounders measured at baseline. Different sensitivity analyses were performed: i) matching at 180 days after cohort entry, ii) intent to treat (ITT) analysis, iii) matching by duration of MET monotherapy, iv) matching by propensity score.

Results: The matched study cohort included 10,600 patients. Overall, 763 TI were observed (4.5/100 person-years; mean follow-up = 1.6 years). The primary analysis showed no difference in time to TI between the two groups (HR = 1.02; 95% CI = 0.88–1.19). Sensitivity analyses confirmed this result, except from the ITT analysis (HR = 1.27; 1.13–1.43).

Conclusion: The use of a DPP4i rather than a SU as add-on to MET monotherapy was not associated with a delay in treatment intensification.

Keywords: type 2 diabetes, DPP4i, sulfonylurea, metformin, treatment intensification, durability, secondary failure, observational study

INTRODUCTION

Diabetes is a chronic metabolic condition causing sustained hyperglycemia due to a deficit of insulin secretion and/or a reduced response of target tissues to this hormone (Merckmanuals, 2021). Type 2 diabetes (T2D), in which insulin-resistance is the predominant pathogenetic mechanism, represents about the 90% of all diabetes cases worldwide (Alberti and Zimmet, 1998). Chronic exposure to hyperglycemia can cause the occurrence of serious and potentially fatal micro- and macrovascular complications (Merckmanuals, 2021). Therefore, patients with T2D are strongly recommended to start a hypoglycemic medication whenever diet and life style modification are not sufficient for maintaining glycemic control (Merckmanuals, 2021; Italian Standards of Medical Care of Diabetes, 2014; American Diabetes Association, 2015).

Metformin is generally considered as the first choice for the initial treatment of T2D (Italian Standards of Medical Care of Diabetes, 2014; Montilla et al., 2014). However, due the progressive nature of the disease, hypoglycemic drugs tend to lose their efficacy over time (i.e., secondary treatment failure) so that treatment intensification might be necessary to maintain the recommended glycemic target (Drucker and Nauck, 2006; Pitocco et al., 2008; White, 2009; Zheng et al., 2018; Kalra et al., 2019).

In addition to traditional second-line non-insulin hypoglycemic drugs such as sulfonylureas, glinides, glitazones, and acarbose, in February 2008 the Italian Healthcare Service approved the reimbursement of the first incretin-based medicines (Azoulay, 2015). The clinical efficacy of this class of drugs in the treatment of T2D relies on the potentiation of the activity of the Glucagon-like peptide 1 (GLP-1), an endogenous hormone belonging to the family of incretin hormones that exerts an important role in the glycemic homeostasis (Schneeweiss et al., 2011). Currently available incretin-based medicines are distinguished in two main groups: GLP-1 analogues (GLP1a) and dipeptidyl peptidase-4 inhibitors (DPP4i). Indeed, DPP4i are the most widely used incretin-based therapies, given their higher convenience of use compared to GLP1a (i.e., oral vs. subcutaneous administration) (Schneeweiss et al., 2011; Italian Standards of Medical Care of Diabetes, 2014; Roberto et al., 2019).

Results from clinical trials have suggested a positive risk/benefit balance of DPP4i in the treatment of T2D (Moride et al., 2005; Schneeweiss et al., 2011). Moreover, results from pre-clinical studies showed a favorable effect on b cell preservation (Deacon, 2004; Drucker and Nauck, 2006). In fact, other than stimulating glucose-dependent insulin secretion, activation of the GLP-1 receptor was found to be associated with increased b cell proliferation and inhibition of b cell apoptosis in different *in vivo* (Edvell and Lindström, 1999; Pospisilik et al., 2002; Pospisilik et al., 2003) and *in vitro* studies (Farilla et al., 2003; Wang et al., 2004). For these reasons, a potential advantage of DPP4i in terms of treatment durability (i.e., time to secondary treatment failure) compared to other hypoglycemic agents was hypothesized (Drucker and Nauck, 2006). However, currently available clinical evidence on DPP4i treatment durability is still scarce and inconclusive (Schneeweiss et al., 2011; Pottegård et al., 2014; Mishriky et al., 2015; Rafaniello et al., 2015; Deacon and Lebovitz, 2016; Foroutan et al., 2016; Mamza et al., 2016; Moreno Juste et al., 2019; Chen et al., 2017). Shedding light on this fundamental aspect of T2D pharmacotherapy can help to better establish the place in therapy of DPP4i compared to other widely used second-line oral hypoglycemic agents such as sulfonylureas (SU) (Mishriky et al., 2015; Deacon and Lebovitz, 2016; Foroutan et al., 2016; Moreno Juste et al., 2019) and have significant impact on drug policies and prescribing recommendations.

Therefore, the aim of this study was to analyse routinely collected administrative data from four Italian geographic areas to verify whether, among patients on metformin (MET) monotherapy for T2D, the add-on of a DPP4i compared to SU was associated with a delay in treatment intensification, which was considered as a proxy of secondary treatment failure.

MATERIALS AND METHODS

Data Source

Italy has a tax-based, universal coverage National Health System organised in three levels: national; regional (21 regions); and local (on average, 10 Local Health Authorities per region). Healthcare is managed, for every inhabitant by the relevant Local Health Authority (LHA) (Trifirò et al., 2019).

This study was based on the analysis of data from four Italian regions, Piedmont (northern Italy), Tuscany and Umbria (central Italy), and one LHA, Caserta (southern Italy) covering an overall source population of around 10 million people (http://demo.istat.it/bil2015/index.html). The four data sources are based on different data banks (Thurin et al., 2021), which collect person-level information on the utilization of healthcare services reimbursed by the National Healthcare Service (NHS) and dispensed to any subject who is resident and registered with a general practitioner in the relevant catchment areas. Through a pseudoanonymized identification code, patient-level information recorded in different registries can be linked. For the purposes of this study, data from the following five data banks were used: 1) inhabitant registry, 2) hospital discharge records, 3) drug registry, 4) reason for exemption from copayment registry, and 5) registry of utilization of secondary care encounters and diagnostic procedures. The drug registry includes dispensing of

prescription drugs intended for outpatient use (e.g., dispensing date, active principle, ATC code, brand name and formulation). The hospital discharge record registry contains information on hospitalization episodes (e.g., date of admission/discharge, discharge diagnoses and procedures code with ICD9-CM terminology). The exemption from copayment registry includes information on the disease that allows patients to be exempt from copayment of a specific list of healthcare services. The registry of secondary care and diagnostic activities include information on the utilization of specialist outpatient encounters, diagnostic tests or procedures (e.g., date, type of specialist visit, test or procedure), but not the results of tests or the diagnosis of the patient. Given the administrative nature of the data source, records are only accepted in the system if all relevant field are correctly filled out.

Selection of the Study Cohort

Patients in the study areas with ≥1 dispensing of a DPP4i or SU (see **Supplementary Appendix S1** for ATC codes) recorded between first of February 2008 and 30 June 2015 were identified (due to difference in data availability, the start date of the recruitment period differed depending on the specific area, see **Supplementary Appendix S2**). The date of the first dispensing of a DPP4i or SU (index prescription) was the cohort entry. Patients aged <18 and with a look-back period <1 year were excluded. To select patients that received a DPP4i or a SU as first add-on to metformin monotherapy, only individuals with ≥1 metformin dispensing recorded at least 60 days before cohort entry were retained in the study cohort (Hayes et al., 2006; Ema, 2021b) (**Supplementary Figure 1**). Moreover, patients had to be persistent to metformin monotherapy (see below for the definition of persistence), and without any record of antidiabetic drug dispensing other than metformin (see **Supplementary Appendix S1**) during the year preceding the index prescription. Patients with a cancer diagnosis (ICD9CM codes: 140–239) recorded at any time before the index prescription were also excluded.

On the basis of the add-on treatment received at cohort entry, patients were classified in the relevant treatment group, i.e., MET + DDP4i or MET + SU.

Study Design and Exposure Definition

This was a retrospective cohort study. Patients in the two groups were followed starting from the index dispensing up to the occurrence of either the study outcome (i.e., treatment intensification) or a censoring event, whichever came first. Events that were considered as censoring criteria were: non-persistence to metformin, non-persistence to the index drug, switch to a different non-insulin hypoglycemic medication (see **Supplementary Appendix S3** for description of the operational definitions of these events), end of study period (31 December 2016), cancer, death, or emigration from the region/LHU of recruitment.

Treatment persistence was defined as the absence of any gap ≥90 days between the end of the estimated duration of a dispensing and the subsequent dispensing date (Greevy et al., 2011). The duration of each observed dispensing was calculated by using the relevant Defined Daily Dose (https://www.whocc.no/atc_ddd_index/).

Each patient on MET + DPP4i treatment was 1:1 matched to patients in the MET + SU treatment group. Matching was performed by age band category (18–44, 45–54, 55–64, 65–74, 75–84, 85 +), sex, calendar year of index prescription and geographical area.

Variables at Baseline

The following variables were measured at baseline (index prescription): age, sex, calendar year of cohort entry, number of encounters with a diabetologist recorded during the year before index prescription. The time elapsed between the first metformin dispensing and the index dispensing (either DPP4i or SU) was used as a proxy of disease duration. For the purpose of sensitivity analyses (see below), this time was also classified either as "definite", for patients with ≥1 year of observation before the first observed metformin dispensing, or "uncertain" (see **Supplymentary Appendix S4**).

Diabetes complications and comorbidities were measured at baseline through diagnoses recorded, either at hospital discharge or as an exemption from copayment, during the year preceding the index prescription (see **Supplementary Appendix S5**).

Similarly, we also measured the use of medications that might affect glycemic control during the year preceding the index prescription (antidepressants, antipsychotics, corticosteroids for systemic use, lipid-lowering drugs, low-dose aspirin, antihypertensive, thiazides, statins, beta-blockers—see **Supplementary Appendix S6**).

Outcomes

The primary outcome was the occurrence of treatment intensification, defined as either the initiation of insulin treatment (first dispensing of insulin) or the add-on of a third non-insulin antidiabetic (see **Supplymentary Appendix S3** for details) (Ema, 2021a; Drucker and Nauck, 2006; Greevy et al., 2011; Anichini et al., 2013; Inzucchi et al., 2015a; Gini et al., 2016). Differently from primary treatment failure, secondary treatment failure occurs when glycemic control is lost after an initial period during which the pharmacological treatment was effective in achieving glycemic control (Pitocco et al., 2008) Since administrative data used for this study do not provide information on glycemic level, distinction between primary treatment failures and early secondary treatment failure was not possible. Therefore, similarly to other previously performed observational studies (Brown et al., 2010), all treatment intensifications occurred during the first 180 days, which are likely to mostly correspond to primary treatment failure, were censored to avoid outcome misclassification.

Statistical Analysis

Survival curves describing the time to treatment intensification in the matched cohort were plotted using the Kaplan-Meier method and the log rank test was used to assess the statistical significance of the difference between groups.

Cox regression models were applied to estimate hazard ratios, with their 95% confidence intervals, and compare the time to

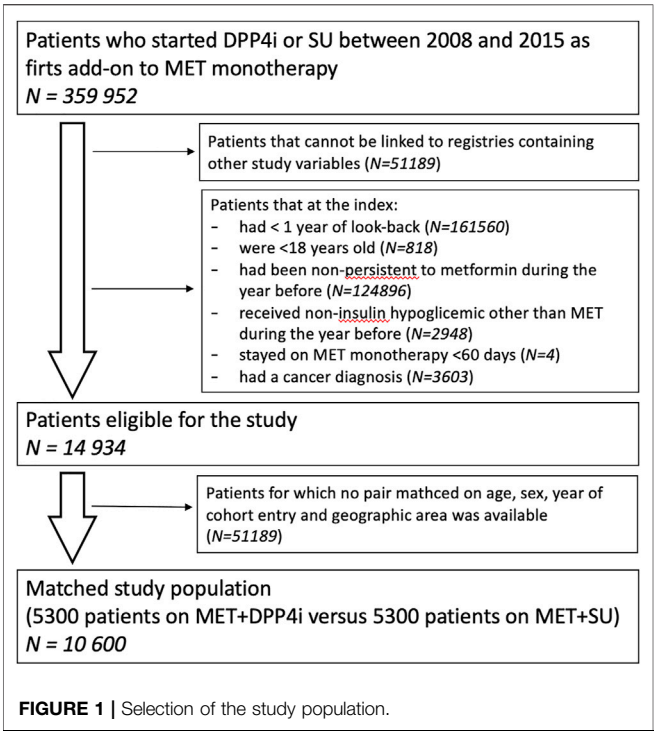


FIGURE 1 | Selection of the study population.

treatment intensification from index prescription in patients treated with MET + DPP4i vs. those in the MET + SU group. All the variables measured at baseline were included in the model to account for their potential confounding effect.

Sensitivity Analyses

In order to evaluate the robustness of our results, we carried out different sensitivity analyses: 1) a Propensity Score-matched analysis with caliper width of 0.1 was performed (Farr et al., 2014). Variables considered for PS included all patients' characteristics measured at baseline. 2) Since disease duration is an important predictor of the durability of the hypoglycemic efficacy of antidiabetic drugs (Wilke et al., 2016), the primary analysis was re-run restricting the study cohort to patients with "definite" time between first antidiabetic dispensing and index drug. 3) Since a significant imbalance in treatment discontinuation probability was observed between the two treatment groups, particularly during the first 6 months from cohort entry (data not shown), start of follow-up time was set at 180 days after index prescription. 4) Finally, an intent-to-treat (ITT) approach was used, in which we did not censored neither for discontinuation nor for switch.

Data Management and Analysis

In order to standardize the process of data extraction and management, each study partners run the open-source software TheMatrix (http://thematrix.isti.cnr.it/) locally. As a result, an aggregated analytical dataset was obtained and shared with all the study participants only after local partner's verification and approval. The Regional Agency for Healthcare Services of Tuscany was responsible for the analyses of the shared analytical dataset. These were performed with the statistical software STATA (version 14).

The full protocol of this study was published in advance to data extraction and analysis on the ENCePP EU PASS Register (freely available at: https://www.encepp.eu/encepp/viewResource.htm?id=28096).

RESULTS

A total of 14,934 patients that received at least one DPP4i or SU dispensing as add-on to prior metformin monotherapy were identified (**Figure 1**). Among them, 6,261 (42%) patients were in treatment with MET + DPP4i, while 8,673 (58%) with MET + SU (**Table 1**). Most of the patients identified were from Tuscany (44.1%) and Piedmont (32.7) (**Supplementary Table 1**). After 1:1 matching by age at index prescription, sex, calendar year of index prescription and geographical area, a cohort of 10,600 patients was included in the analysis (5,300 patients in each group). Overall, most of the patients in the matched study cohort were male (57.2%) and the great majority (81.5%) of the enrolled patients were aged ≥55 years (**Table 1**). Patients in treatment with MET + SU compared with MET + DDP4i users, differed in utilization of some medications, e.g., systemic corticosteroids (MET + iDPP4 = 11.5% vs. MET + SU = 14%) and lipid lowering medications (MET + iDPP4 = 63% vs. MET + SU = 55%).

The average available time of observation time for patients in the cohort was about 4 years and a half, however the application of the censoring criteria resulted in a mean follow-up time of 1.9 years for patients in treatment with MET + DDP4i and 1.2 years for those treated with MET + SU. The main causes of censoring were related to discontinuation of either the index drug or MET, with a more frequent occurrence for patients in treatment with MET + SU (overall 76.5%) compared to MET + DD4i (overall 66.8%) (**Supplementary Table 2**).

A total of 763 treatment intensification was observed, corresponding to an incidence rate of 4.5 per 100 person-years. Kaplan-Meier survival curve describing time to treatment intensification showed no significant differences ($p = 0.89$) in time to treatment intensification between the two matched groups (**Figure 2**). Cox regression yielded comparable results to those obtained with the Kaplan-Meier method (**Table 2**) showing no significant differences between the two groups in terms of time to treatment intensification (HR: 1.02; 95%CI:0.88–1.19). The regression analysis also showed that patients aged 55–84 years had a lower risk for treatment intensification compared to younger patients aged 18–44 years (**Table 2**). Moreover, the risk of treatment intensification appeared to increase along with the time from first metformin dispensing. A positive association with treatment intensification was also observed in patients using antidepressants (adj HR: 1.25; 95%CI: 1.02–1.54) and antihypertensive drugs (adj HR: 1.28; 95%CI: 1.07–1.54) compared to non-users. Finally, patients from Piedmont and Umbria, respectively were less likely to receive a treatment intensification compared to those from Caserta.

Overall, results from the sensitivity analyses (**Table 3**) were in line with those from the primary analyses and did not highlighted

TABLE 1 | Cohort characteristics before and after matching.

	Pre-matching		Post-matching	
	DPP4i (6,261)	SU (8,673)	DPP4i (5,300)	SU (5,300)
	N (%)	N (%)	N (%)	N (%)
Women	2,609 (41.7)	4,110 (47.4)	2,268 (42.8)	2,268 (42.8)
Age band				
18–44	275 (4.4)	297 (3.4)	204 (3.8)	204 (3.8)
45–54	1,080 (17.2)	1,013 (11.7)	775 (14.6)	775 (14.6)
55–64	2,103 (33.6)	2,259 (26.1)	1712 (32.3)	1712 (32.3)
65–74	1930 (30.8)	2,921 (33.7)	1773 (33.4)	1773 (33.4)
75–84	774 (12.4)	1831 (21.1)	748 (14.1)	748 (14.1)
85+	99 (1.6)	352 (4.1)	88 (1.7)	88 (1.7)
Cohort entry				
2008	82 (1.3)	755 (8.7)	81 (1.5)	81 (1.5)
2009	187 (3.0)	767 (8.8)	186 (3.5)	186 (3.5)
2010	338 (5.4)	802 (9.3)	338 (6.4)	338 (6.4)
2011	706 (11.3)	738 (8.5)	559 (10.6)	559 (10.6)
2012	933 (14.9)	804 (9.3)	695 (13.1)	695 (13.1)
2013	1715 (27.4)	1883 (21.7)	1,416 (26.7)	1,416 (26.7)
2014	1,282 (20.5)	1974 (22.8)	1,222 (23.1)	1,222 (23.1)
2015	1,018 (16.3)	950 (10.9)	803 (15.1)	803 (15.1)
Time since 1st MET				
0	283 (4.5)	410 (4.7)	188 (3.6)	252 (4.8)
1	1,012 (16.2)	1,309 (15.1)	768 (14.5)	815 (15.4)
2	902 (14.4)	1,342 (15.5)	746 (14.1)	826 (15.9)
3	1,388 (22.2)	1791 (20.7)	1,218 (23.0)	1,156 (21.8)
4+	2,676 (42.7)	3,821 (44.1)	2,380 (44.9)	2,251 (42.5)
Diabetes-related comorbidities				
Acute myocardial infarction	33 (0.5)	79 (0.9)	32 (0.6)	48 (0.9)
Acute ischemic heart disease	37 (0.6)	50 (0.6)	33 (0.6)	22 (0.4)
Angina pectoris	23 (0.4)	41 (0.5)	21 (0.4)	25 (0.5)
Operations on vessel of heart	72 (1.2)	111 (1.3)	65 (1.2)	64 (1.2)
Cerebrovascular diseases	27 (0.4)	64 (0.7)	24 (0.5)	34 (0.6)
Retinopathy	4 (0.1)	3 (<0.0)	3 (0.1)	1 (<0.0)
Diabetes with ophthalmic manifestations	5 (0.1)	1 (<0.0)	4 (0.1)	1 (<0.0)
Diabetes with renal manifestations	10 (0.2)	8 (0.1)	8 (0.2)	4 (0.1)
Acute kidney failure	11 (0.2)	14 (0.2)	11 (0.2)	5 (0.1)
Diabetes with peripheral circulatory disorders	38 (0.6)	65 (0.8)	36 (0.7)	42 (0.8)
Ulcer of lower limbs, except pressure ulcer	5 (0.0)	8 (0.1)	5 (0.1)	6 (0.1)
Concomitant Pharmacotherapies				
Antidepressants	815 (13.0)	1,468 (16.9)	706 (13.3)	842 (15.9)
Corticosteroids for systemic use	699 (11.2)	1,249 (14.4)	607 (11.5)	740 (14.0)
Lipid lowering drugs	3,897 (62.3)	4,658 (53.7)	3,355 (63.3)	2,921 (55.1)
Anticoagulants	656 (10.5)	1,101 (12.7)	581 (11.0)	604 (11.4)
Antiplatelets	2,497 (39.9)	3,626 (41.8)	2,187 (41.3)	2,100 (39.6)
Beta blockers	2009 (32.1)	2,781 (32.1)	1719 (32.4)	1708 (32.2)
Antihypertensives and/or diuretics	1,379 (22.0)	2,442 (28.2)	1,207 (22.8)	1,331 (25.1)
Dihydropyridine CCB	1,407 (22.5)	2,116 (24.4)	1,208 (22.8)	1,244 (23.5)
Non Dihydropyridine CCB	158 (2.5)	247 (2.9)	142 (2.7)	130 (2.5)
Angiotensin receptor blockers and ACE-I	4,207 (67.2)	5,859 (67.6)	3,596 (67.9)	3,521 (66.4)
Antipsychotics	139 (2.2)	304 (3.5	110 (2.1)	193 (3.6)

MET, metformin; DDP4i = dipeptidyl peptidase inhibitor; SU, sulfonylurea.

differences in rate of treatment intensification in patients treated with MET + DPP4i vs. MET + SU, with the exceptions of the ITT analysis (adj HR:1.27; 95%CI: 1.13–1.43), where an increased risk of treatment intensification was observed among DPP4i users.

DISCUSSION

In this retrospective cohort study based on administrative healthcare data, the add-on of a DPP4i rather than a SU to MET monotherapy was not associated with a delay of the subsequent treatment intensification. In our cohort of T2D patients, more than half of patients in both treatment groups discontinued the assigned anti-diabetic treatment during follow-up. The observed frequency of discontinuation was consistent with results reported from previous studies (Farr et al., 2014). Side effects, mostly gastrointestinal, and efficacy issues usually represents the main reasons for discontinuation (Farr et al., 2014; Roborel de Climens et al., 2020). In particular, in accordance with the evidences from the literature (Rathmann

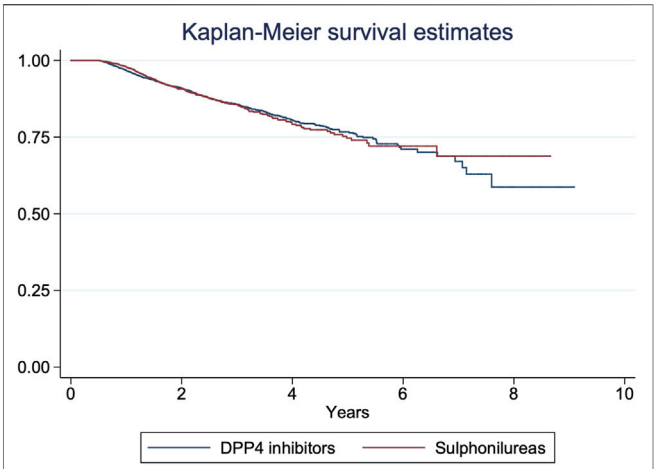


FIGURE 2 | Kaplan-Meier survival estimate in the matched study cohort.

et al., 2013; Peng et al., 2016; Bloomgarden et al., 2017), in the present study cohort, discontinuation occurred more frequently among patients on MET + SU. A previous retrospective cohort study based on administrative claim-database (Bloomgarden et al., 2017) also found that patients on MET + sitagliptin had both higher adherence and persistence when compared to patients on MET + SU. The known higher risk of hypoglycemic events associated to SU represent a possible explanation for the lower adherence and persistence observed among SU users compared to DPP4i users (Inzucchi et al., 2015b; Valensi et al., 2015; Foroutan et al., 2016). In the present study, however, deviations from the index treatment, like discontinuation or switch, caused the censoring of patients. In particular, this approach allowed controlling for the higher probability of receiving a treatment intensification expected for patients treated with MET + DPP4i compared to those on MET + SU. In fact, due the special reimbursement access criteria applied to DPP4i by the Italian National Healthcare System (Montilla et al., 2014), patients receiving DPP4i are expected to be more strictly monitored than those on SU so that a timely detection of a secondary treatment failure and a consequent treatment intensification is more likely occur.

During the last 2 decades, in many countries, SU have been the most widely used second-line non-insulin hypoglycemic medications (Mishriky et al., 2015; Deacon and Lebovitz, 2016; Foroutan et al., 2016; Moreno Juste et al., 2019). Nevertheless, current guidelines recommend preferring the use of SU as add-on to metformin monotherapy only if costs represent a major issue (Davies et al., 2018). In fact, despite the longer clinical experience available for SU and its comparable hypoglycemic effect with respect to the newer DPP4i, the latter show important advantages in terms of risk of hypoglycemic events and impact on body weight (Inzucchi et al., 2015b; Foroutan et al., 2016).

As for the comparative durability of the hypoglycemic effect of DPP4i vs. SU, instead, current clinical evidences are still poor and inconclusive (Mamza et al., 2016; Chen et al., 2017; Inzucchi et al., 2015a). A meta-analysis of eight double-blind randomized clinical trial reported that MET + DPP4i were associated with significantly smaller increases in the HbA1c level from 24–28–104 weeks compared with MET + SU (mean difference: −0.16%, 95%CI: −0.21 to −0.11; $p < 0.001$). However, on one hand the high rate of lost to follow-up in the included studies threaten results validity while, on the other hand, the clinical relevance of these findings is likely to be negligible (Chen et al., 2017).

Inzucchi et al. (Inzucchi et al., 2015a) conducted a retrospective observational study using a US data source of

TABLE 2 | Results from the multivariate Cox regression model.

	adj HR*	[95%CI]	
MET + iDPP4	Ref	Ref	Ref
MET + SU	1.02	0.88	1.19
Men	Ref	Ref	Ref
Women	0.93	0.80	1.08
Age band			
18–44	Ref	Ref	Ref
45–54	0.86	0.61	1.22
55–64	0.57	0.41	0.80
65–74	0.45	0.32	0.64
75–84	0.43	0.28	0.64
85+	0.74	0.37	1.48
Cohort entry			
2008	Ref	Ref	Ref
2009	1.50	0.83	2.69
2010	1.16	0.66	2.04
2011	1.22	0.71	2.11
2012	1.13	0.65	1.95
2013	0.93	0.53	1.62
2014	0.90	0.51	1.57
2015	0.61	0.33	1.11
Geographical area			
Caserta	Ref	Ref	Ref
Piemonte	1.38	1.03	1.87
Toscana	1.02	0.79	1.32
Umbria	1.73	1.25	2.41
Time since 1st MET			
0	Ref	Ref	Ref
1	1.34	0.86	2.09
2	1.54	0.98	2.40
3	1.62	1.04	2.52
4+	1.66	1.08	2.57
Diabetes-related comorbidities			
Acute myocardial infarction	0.65	0.14	3.08
Acute ischemic heart disease	1.27	0.31	5.25
Angina pectoris	1.65	0.59	4.64
Cerebrovascular diseases	1.38	0.50	3.78
Diabetes with neurological manifestations	2.94	0.72	12.08
Diabetes with peripheral circulatory disorders	0.24	0.03	1.77
Operations on vessel of heart	0.69	0.22	2.13
Concomitant pharmacotherapies			
Antidepressants	1.25	1.02	1.54
Corticosteroids for systemic use	0.95	0.75	1.21
Lipid lowering drugs	0.95	0.82	1.11
Anticoagulants	1.02	0.79	1.32
Antiplatelets	1.10	0.93	1.30
Beta blockers	1.08	0.92	1.28
Antihypertensives and/or diuretics	1.28	1.07	1.54
Dihydropyridine CCB	1.05	0.88	1.26
Non Dihydropyridine CCB	1.46	0.96	2.22
Angiotensin receptor blockers and ACE-I	1.00	0.85	1.17
Antipsychotics	1.26	0.83	1.90

**adjusted hazard ratio for all covariates measured at baseline.*
MET, metformin; DDP4i = dipeptidyl peptidase inhibitor; SU, sulfonylurea.

TABLE 3 | Risk of treatment intensification in patients using DDP4i compared to those using sulfonylurea: sensitivity analyses.

Analysis	adj HR[a]	[95%CI]
Matching by propensity score	0.93	0.81–1.08
Restriction to patients with "definite" time between first antidiabetic dispensing and index prescription	1.18	0.97–1.43
Start of follow-up time set at 180 days after index prescription	0.96	0.83–1.12
intent-to-treat approach	1.27	1.13–1.43

[a]*Adjusted hazard ratio for all covariates measured at baseline.*

electronic medical records. The authors compared the time to insulin initiation among T2D patients in a propensity score matched cohort of 3,864 subjects on MET + SU and an equal number of patients on MET + sitagliptin. Findings from this study suggested that patients treated with MET + sitagliptin had a lower risk of insulin initiation compared to those treated with MET + SU (adj HR: 0.761; 95%CI: 0.646–0.897), which become statistically significant after 4 years since study entry. However, exposure misclassification might have biased the results, as the authors could not ascertain if a patient was continuously treated with the index therapy beyond 90 days after enrollment, as required by the study design, or if they discontinued or switched therapy (Inzucchi et al., 2015a). Montivida and others performed an observational retrospective cohort study using the US Centricity Electronic Medical Records stratifying the study population according to the HbA1c levels recorded at time of second-line antidiabetic drug initiation (i.e., HbA1c 7.5–7.9%, 8–9%, 9.1–12%, >12%). The authors reported that patients treated with second-line DPP4i having a baseline HbA1c levels between 7.5% and 12% had slightly higher probability of sustaining glycemic control over 2 years without further intensification than those treated with SU (Montvida et al., 2018). One of the major limitations of this study was the absence of information on treatment adherence during follow-up. Another observational retrospective cohort study from Mamza et al. (Mamza et al., 2016) found that, T2D patients on MET + DPP4i were more likely to experience a substitution or intensification of treatment with a third agent at HbA1c ≥ 7.5% during follow-up compared to those on MET + SU (adjusted HR, 1.58; 95%CI: 1.48–1.68). The inconsistency of results reported by Mamza and others compared to the studies reported above as well as the analyses presented in this paper is likely to be explained by differences in study design and outcome definition. Moreover, as acknowledged by study authors, patients on MET + SU and MET + DPP4i were not required to have comparable persistence or adherence to the treatment during follow-up (Okemah et al., 2018).

Strengths and Limitations

One of the main strengths of the present study is represented by the emulation of a "per protocol" approach for which deviations from the index treatment like switch and treatment discontinuation caused the censoring of patients from follow-up. As demonstrated by the results of the ITT analysis, this approach allowed limiting the impact of the special reimbursement access criteria applied in Italy to DPP4i, which are expected to favour the timely detection of secondary treatment failure in patients treated with these drugs and, thus, differentially affect the probability of receiving a treatment intensification in the two exposure groups. Moreover, estimates of relative risk were statistically adjusted for several baseline characteristics that can act as confounders. In particular, other than concomitant pharmacotherapies and diabetes-related comorbidities, the time from first metformin dispensing was also included in the model as a proxy of disease duration. Another strength of our study concerns the use of multiple population-based administrative healthcare data sources from four different Italian geographic areas covering about 15% of the whole Italian population. This resulted in a large sample size and a higher generalizability of study findings. However, there are also limitations that should be considered for the correct interpretation of study results. First, the use of administrative healthcare data does not allow to control for clinical characteristics like HbA1c levels, body mass index and physical activity, which are well known risk factors for secondary treatment failure (Kalra et al., 2019). Also, it is noteworthy that secondary treatment failure is actually diagnosed based on periodic HbA1c measurements and that we used the addition of a third non-insulin antidiabetic medication or insulin after at least 180 days following treatment initiation as the study outcome. Although its validity as a proxy of secondary treatment failure was not assessed in the present study, we expect a high positive predictive value, also due to the exclusion of switches to different medications from the outcome definition, which may reflect tolerability rather than efficacy issues (Ekström et al., 2015). Nevertheless, we cannot exclude that a minority of the treatment intensifications observed even after 180 days from treatment initiation were actually primary treatment failures detected with delay. Another study limitation concerns the possible misclassification of exposure. This is intrinsic to the nature of the observational data used for the study. First, dispensing data do not provide information on the actual intake of the dispensed medication. Second, only dispensings of prescription drugs reimbursed by the NHS are captured. Given the chronic nature of diabetes and the fully-reimbursed healthcare assistance provided by the Italian NHS to patients with T2D, exposure misclassification in this study was likely minor and non-differential, although we cannot exclude a possible bias toward the null. Finally, given the observational nature of this study, residual confounder due the differential management and care of patients in the two

treatment groups might have possibly affected the results and artefactually increased the risk of treatment intensification for patients on DPP4i relatively to those on SU.

In conclusion, this study found that in patients with T2D from four Italian geographical areas the add-on of a DPP4i rather than a SU to MET monotherapy was not associated with a delay of the subsequent treatment intensification. This study adds further insights to the body of evidence concerning the real-world long-term comparative durability of these two widely used second-line hypoglycemic agents. However, given the limitations related to the observational nature of the study and the heterogeneity of the available clinical evidence, further studies on this topic are warranted to better define the place in therapy and prescribing recommendations for DPP4i with respect to SU, as well as to other available second-line medications for T2D.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The datasets presented in this article are not readily available because of the privacy legislation. Requests to access the datasets should be directed to the corresponding author. Requests to access these datasets should be directed to giuseppe.roberto@ars.toscana.it.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FB, GR and RG conceived the study. GR, RG, FB-A, EP and PF developed to the study design and the statistical analysis plan. RG performed central data management and analysis. RG, RDC e VI transform local data in common format e run the script for the extraction of the analytical dataset. GR drafted the manuscript with the contribution of AG, AP e FB-A. All authors reviewed and approved all steps of the execution of the study including the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.871052/full#supplementary-material

REFERENCES

Alberti, K. G., and Zimmet, P. Z. (1998). Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus Provisional Report of a WHO Consultation. *Diabet Med.* 15 (7), 539–553. doi:10.1002/(SICI)1096-9136(199807)15:7<539:AID-DIA668>3.0.CO;2-S

Anichini, R., Cosimi, S., Di Carlo, A., Orsini, P., De Bellis, A., Seghieri, G., et al. (2013). Gender Difference in Response Predictors after 1-year Exenatide Therapy Twice Daily in Type 2 Diabetic Patients: a Real World Experience. *Diabetes Metab. Syndr. Obes.* 6, 123–129. doi:10.2147/DMSO.S42729

American Diabetes Association (2015). Standards of Medical Care in Diabetes--2015: Summary of Revisions. *Diabetes Care* 38 (Suppl. l). S4. doi:10.2337/dc15-S003

Azoulay, L. (2015). Incretin-based Drugs and Adverse Pancreatic Events: Almost a Decade Later and Uncertainty Remains. *Diabetes Care* 38 (6), 951–953. doi:10.2337/dc15-0347

Bloomgarden, Z. T., Tunceli, K., Liu, J., Brodovicz, K. G., Mavros, P., Engel, S. S., et al. (2017). Adherence, Persistence, and Treatment Discontinuation with Sitagliptin Compared with Sulfonylureas as Add-Ons to Metformin: A Retrospective Cohort Database Study. *J. Diabetes* 9 (7), 677–688. doi:10.1111/1753-0407.12461

Brown, J. B., Conner, C., and Nichols, G. A. (2010). Secondary Failure of Metformin Monotherapy in Clinical Practice. *Diabetes Care* 33 (3), 501–506. doi:10.2337/dc09-1749

Byetta - Summary of Product Characteristics, Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf. (Accessed November 24, 2021)

Chen, K., Kang, D., Yu, M., Zhang, R., Zhang, Y., Chen, G., et al. (2017). Direct Head-To-Head Comparison of Glycaemic Durability of Dipeptidyl Peptidase-4 Inhibitors and Sulphonylureas in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis of Long-Term Randomized Controlled Trials. Available at: https://pubmed.ncbi.nlm.nih.gov/29095568/(Accessed November 24, 2021).

Davies, M. J., D'Alessio, D. A., Fradkin, J., Kernan, W. N., Mathieu, C., Mingrone, G., et al. (2018). Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 41 (12), 2669–2701. doi:10.2337/dci18-0033

Deacon, C. F., and Lebovitz, H. E. (2016). Comparative Review of Dipeptidyl Peptidase-4 Inhibitors and Sulphonylureas. *Diabetes Obes. Metab.* 18 (4), 333–347. doi:10.1111/dom.12610

Deacon, C. F. (2004). Therapeutic Strategies Based on Glucagon-like Peptide 1. *Diabetes* 53 (9), 2181–2189. doi:10.2337/diabetes.53.9.2181

Drucker, D. J., and Nauck, M. A. (2006). The Incretin System: Glucagon-like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes. *Lancet* 368 (9548), 1696–1705. doi:10.1016/S0140-6736(06)69705-5

Edvell, A., and Lindström, P. (1999). Initiation of Increased Pancreatic Islet Growth in Young Normoglycemic Mice (Umeå +/?)*. *Endocrinology* 140 (2), 778–783. doi:10.1210/endo.140.2.6514

Ekström, N., Svensson, A. M., Miftaraj, M., Andersson Sundell, K., Cederholm, J., Zethelius, B., et al. (2015). Durability of Oral Hypoglycemic Agents in Drug Naïve Patients with Type 2 Diabetes: Report from the Swedish National Diabetes Register (NDR). *BMJ Open Diabetes Res. Care* 3 (1), e000059. doi:10.1136/bmjdrc-2014-000059

Farilla, L., Bulotta, A., Hirshberg, B., Li Calzi, S., Khoury, N., Noushmehr, H., et al. (2003). Glucagon-like Peptide 1 Inhibits Cell Apoptosis and Improves Glucose Responsiveness of Freshly Isolated Human Islets. *Endocrinology* 144 (12), 5149–5158. doi:10.1210/en.2003-0323

Farr, A. M., Sheehan, J. J., Curkendall, S. M., Smith, D. M., Johnston, S. S., and Kalsekar, I. (2014). Retrospective Analysis of Long-Term Adherence to and Persistence with DPP-4 Inhibitors in US Adults with Type 2 Diabetes Mellitus. *Adv. Ther.* 31 (12), 1287–1305. doi:10.1007/s12325-014-0171-3

Foroutan, N., Muratov, S., and Levine, M. (2016). Safety and Efficacy of Dipeptidyl Peptidase-4 Inhibitors vs Sulfonylurea in Metformin-Based Combination Therapy for Type 2 Diabetes Mellitus: Systematic Review

and Meta-Analysis. *Clin. Invest. Med.* 39 (2), E48–E62. doi:10.25011/cim.v39i2.26481

Gini, R., Schuemie, M., Brown, J., Ryan, P., Vacchi, E., Coppola, M., et al. (2016). Data Extraction and Management in Networks of Observational Health Care Databases for Scientific Research: A Comparison of EU-ADR, OMOP, Mini-Sentinel and MATRICE Strategies. *EGEMS Wash. DC* 4 (1), 1189. doi:10.13063/2327-9214.1189

Greevy, R. A., Huizinga, M. M., Roumie, C. L., Grijalva, C. G., Murff, H., Liu, X., et al. (2011). Comparisons of Persistence and Durability Among Three Oral Antidiabetic Therapies Using Electronic Prescription-Fill Data: the Impact of Adherence Requirements and Stockpiling. *Clin. Pharmacol. Ther.* 90 (6), 813–819. doi:10.1038/clpt.2011.228

Hayes, R. P., Bowman, L., Monahan, P. O., Marrero, D. G., and McHorney, C. A. (2006). Understanding Diabetes Medications from the Perspective of Patients with Type 2 Diabetes: Prerequisite to Medication Concordance. *Diabetes Educ.* 32 (3), 404–414. doi:10.1177/0145721706288182

Inzucchi, S. E., Tunceli, K., Qiu, Y., Rajpathak, S., Brodovicz, K. G., Engel, S. S., et al. (2015a). Progression to Insulin Therapy Among Patients with Type 2 Diabetes Treated with Sitagliptin or Sulphonylurea Plus Metformin Dual Therapy. *Diabetes Obes. Metab.* 17 (10), 956–964. doi:10.1111/dom.12489

Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., et al. (2015b). Management of Hyperglycaemia in Type 2 Diabetes, 2015: a Patient-Centred Approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 38 (1), 140. doi:10.2337/dc14-2441

Italian Standards of Medical Care of Diabetes (2014). Associazione Medici Diabetologici, Available at: http://www.gdm1.org/eventi/STANDARD_2014_May28.pdf (Accessed November 24, 2021).

Kalra, S., Kamaruddin, N. A., Visvanathan, J., and Santani, R. (2019). Defining Disease Progression and Drug Durability in Type 2 Diabetes Mellitus. *Eur. Endocrinol.* 15 (2), 67–69. doi:10.17925/EE.2019.15.2.67

Mamza, J., Mehta, R., Donnelly, R., and Idris, I. (2016). Important Differences in the Durability of Glycaemic Response Among Second-Line Treatment Options when Added to Metformin in Type 2 Diabetes: a Retrospective Cohort Study. *Ann. Med.* 48 (4), 224–234. doi:10.3109/07853890.2016.1157263

Mishriky, B. M., Cummings, D. M., and Tanenberg, R. J. (2015). The Efficacy and Safety of DPP4 Inhibitors Compared to Sulfonylureas as Add-On Therapy to Metformin in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Diabetes Res. Clin. Pract.* 109 (2), 378–388. doi:10.1016/j.diabres.2015.05.025

Montilla, S., Marchesini, G., Sammarco, A., Trotta, M. P., Siviero, P. D., Tomino, C., et al. (2014). Drug Utilization, Safety, and Effectiveness of Exenatide, Sitagliptin, and Vildagliptin for Type 2 Diabetes in the Real World: Data from the Italian AIFA Anti-diabetics Monitoring Registry. *Nutr. Metab. Cardiovasc. Dis.* 24 (12), 1346–1353. doi:10.1016/j.numecd.2014.07.014

Montvida, O., Shaw, J. E., Blonde, L., and Paul, S. K. (2018). Long-term Sustainability of Glycaemic Achievements with Second-Line Antidiabetic Therapies in Patients with Type 2 Diabetes: A Real-World Study. *Diabetes Obes. Metab.* 20 (7), 1722–1731. doi:10.1111/dom.13288

Moreno Juste, A., Menditto, E., Orlando, V., Monetti, V. M., Gimeno Miguel, A., González Rubio, F., et al. (2019). Treatment Patterns of Diabetes in Italy: A Population-Based Study. *Front. Pharmacol.* 10, 870. doi:10.3389/fphar.2019.00870

Moride, Y., Ducruet, T., Boivin, J. F., Moore, N., Perreault, S., and Zhao, S. (2005). Prescription Channeling of COX-2 Inhibitors and Traditional Nonselective Nonsteroidal Anti-inflammatory Drugs: a Population-Based Case-Control Study. *Arthritis Res. Ther.* 7 (2), R333–R342. doi:10.1186/ar1488

Okemah, J., Peng, J., and Quiñones, M. (2018). Addressing Clinical Inertia in Type 2 Diabetes Mellitus: A Review. *Adv. Ther.* 35 (11), 1735–1745. doi:10.1007/s12325-018-0819-5

Peng, X., Jiang, D., Liu, D., Varnado, O. J., and Bae, J. P. (2016). Treatment Progression in Sulfonylurea and Dipeptidyl Peptidase-4 Inhibitor Cohorts of Type 2 Diabetes Patients on Metformin. *Patient Prefer Adherence* 10, 1539–1546. doi:10.2147/PPA.S109664

Pitocco, D., Valle, D., Rossi, A., and Gentilella, R. (2008). Unmet Needs Among Patients with Type 2 Diabetes and Secondary Failure to Oral Anti-diabetic Agents. *J. Endocrinol. Invest.* 31 (4), 371–379. doi:10.1007/BF03346373

Pospisilik, J. A., Stafford, S. G., Demuth, H. U., Brownsey, R., Parkhouse, W., Finegood, D. T., et al. (2002). Long-term Treatment with the Dipeptidyl Peptidase IV Inhibitor P32/98 Causes Sustained Improvements in Glucose Tolerance, Insulin Sensitivity, Hyperinsulinemia, and Beta-Cell Glucose Responsiveness in VDF (Fa/fa) Zucker Rats. *Diabetes* 51 (4), 943–950. doi:10.2337/diabetes.51.4.943

Pospisilik, J. A., Martin, J., Doty, T., Ehses, J. A., Pamir, N., Lynn, F. C., et al. (2003). Dipeptidyl Peptidase IV Inhibitor Treatment Stimulates Beta-Cell Survival and Islet Neogenesis in Streptozotocin-Induced Diabetic Rats. *Diabetes* 52 (3), 741–750. doi:10.2337/diabetes.52.3.741

Pottegård, A., Bjerregaard, B. K., Larsen, M. D., Larsen, K. S., Hallas, J., Knop, F. K., et al. (2014). Use of Exenatide and Liraglutide in Denmark: a Drug Utilization Study. *Eur. J. Clin. Pharmacol.* 70 (2), 205–214. doi:10.1007/s00228-013-1595-4

Rafaniello, C., Arcoraci, V., Ferrajolo, C., Sportiello, L., Sullo, M. G., Giorgianni, F., et al. (2015). Trends in the Prescription of Antidiabetic Medications from 2009 to 2012 in a General Practice of Southern Italy: a Population-Based Study. *Diabetes Res. Clin. Pract.* 108 (1), 157–163. doi:10.1016/j.diabres.2014.12.007

Rathmann, W., Kostev, K., Gruenberger, J. B., Dworak, M., Bader, G., and Giani, G. (2013). Treatment Persistence, Hypoglycaemia and Clinical Outcomes in Type 2 Diabetes Patients with Dipeptidyl Peptidase-4 Inhibitors and Sulphonylureas: a Primary Care Database Analysis. *Diabetes Obes. Metab.* 15 (1), 55–61. doi:10.1111/j.1463-1326.2012.01674.x

Roberto, G., Barone-Adesi, F., Giorgianni, F., Pizzimenti, V., Ferrajolo, C., Tari, M., et al. (2019). Patterns and Trends of Utilization of Incretin-Based Medicines between 2008 and 2014 in Three Italian Geographic Areas. *BMC Endocr. Disord.* 19 (1), 18. doi:10.1186/s12902-019-0334-y

Roborel de Climens, A., Pain, E., Boss, A., and Shaunik, A. (2020). Understanding Reasons for Treatment Discontinuation, Attitudes and Education Needs Among People Who Discontinue Type 2 Diabetes Treatment: Results from an Online Patient Survey in the USA and UK. *Diabetes Ther.* 11 (8), 1873–1881. doi:10.1007/s13300-020-00843-9

Schneeweiss, S., Gagne, J. J., Glynn, R. J., Ruhl, M., and Rassen, J. A. (2011). Assessing the Comparative Effectiveness of Newly Marketed Medications: Methodological Challenges and Implications for Drug Development. *Clin. Pharmacol. Ther.* 90 (6), 777–790. doi:10.1038/clpt.2011.235

The Merk Manual - Professional version, Available at: http://www.merckmanuals.com/professional (Accessed November 24, 2021).

Thurin, N. H., Pajouheshnia, R., Roberto, G., Dodd, C., Hyeraci, G., Bartolini, C., et al. (2021). From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety during Pregnancy and Breastfeeding. *Clin. Pharmacol. Ther.* 111 (1), 321–331. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/cpt.2476 (Accessed November 30, 2021). doi:10.1002/cpt.2476

Trifirò, G., Gini, R., Barone-Adesi, F., Beghi, E., Cantarutti, A., Capuano, A., et al. (2019). The Role of European Healthcare Databases for Post-Marketing Drug Effectiveness, Safety and Value Evaluation: Where Does Italy Stand? *Drug Saf.* 42 (3), 347–363. doi:10.1007/s40264-018-0732-5

Valensi, P., de Pouvourville, G., Benard, N., Chanut-Vogel, C., Kempf, C., Eymard, E., et al. (2015). Treatment Maintenance Duration of Dual Therapy with Metformin and Sitagliptin in Type 2 Diabetes: The ODYSSEE Observational Study. *Diabetes Metab.* 41 (3), 231–238. doi:10.1016/j.diabet.2015.03.007

Victoza - Summary of Product Characteristics, Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf (Accessed November 24, 2021).

Wang, Q., Li, L., Xu, E., Wong, V., Rhodes, C., and Brubaker, P. L. (2004). Glucagon-like Peptide-1 Regulates Proliferation and Apoptosis via Activation of Protein Kinase B in Pancreatic INS-1 Beta Cells. *Diabetologia* 47 (3), 478–487. doi:10.1007/s00125-004-1327-5

White, J. (2009). Efficacy and Safety of Incretin Based Therapies: Clinical Trial Data. *J. Am. Pharm. Assoc. (2003)* 49 (Suppl. 1), S30–S40. doi:10.1331/JAPhA.2009.09079

Wilke, T., Mueller, S., Groth, A., Berg, B., Fuchs, A., Sikirica, M., et al. (2016). Non-Persistence and Non-adherence of Patients with Type 2 Diabetes Mellitus in

Therapy with GLP-1 Receptor Agonists: A Retrospective Analysis. *Diabetes Ther.* 7 (1), 105–124. doi:10.1007/s13300-015-0149-4

Zheng, Y., Ley, S. H., and Hu, F. B. (2018). Global Aetiology and Epidemiology of Type 2 Diabetes Mellitus and its Complications. *Nat. Rev. Endocrinol.* 14 (2), 88–98. doi:10.1038/nrendo.2017.151

Conflict of Interest: GR, AG, CB and RG are employed by Agenzia regionale di sanitá della Toscana (ARS), a public health agency that conducts or participates in pharmacoepidemiology studies compliant with the ENCePP Code of Conduct. The budget of ARS is partially sustained by such studies.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 22 June 2022
doi: 10.3389/fphar.2022.878092

A Prescribing Cascade of Proton Pump Inhibitors Following Anticholinergic Medications in Older Adults With Dementia

Shanna C. Trenaman[1†], Austin Harding[2], Susan K. Bowles[1,2,3†], Susan A. Kirkland[1,4] and Melissa K. Andrew[1,2†]*

[1]Department of Medicine, Dalhousie University, Halifax, NS, Canada, [2]Nova Scotia Health, Halifax, NS, Canada, [3]College of Pharmacy, Dalhousie University, Halifax, NS, Canada, [4]Department of Community Health and Epidemiology, Dalhousie University, Halifax, NS, Canada

OPEN ACCESS

Edited by:
Andrea Burden,
ETH Zürich, Switzerland

Reviewed by:
Daniel Harwood,
South London and Maudsley NHS Foundation Trust, United Kingdom
Malinee Neelamegam,
University of North Texas Health Science Center, United States

***Correspondence:**
Shanna C. Trenaman
shanna.trenaman@dal.ca

†ORCID:
Shanna C. Trenaman
orcid.org/0000-0002-7982-4437
Susan K. Bowles
orcid.org/0000-0003-0821-3222
Melissa K. Andrew
orcid.org/0000-0001-7514-8972

Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: *17 February 2022*
Accepted: *30 May 2022*
Published: *22 June 2022*

Citation:
Trenaman SC, Harding A, Bowles SK, Kirkland SA and Andrew MK (2022) A Prescribing Cascade of Proton Pump Inhibitors Following Anticholinergic Medications in Older Adults With Dementia. Front. Pharmacol. 13:878092. doi: 10.3389/fphar.2022.878092

Introduction: Prescribing cascade refers to use of a medication to treat a drug-related adverse event. Prescribing cascades increase medication use, cost, and risk of adverse events.

Objective: Our objective was to use administrative health data to identify whether use of medications from the anticholinergic cognitive burden scale was associated with proton pump inhibitor (PPI) prescribing consistent with a prescribing cascade in older adults with dementia.

Method: The cohort was comprised of Nova Scotia Seniors' Pharmacare beneficiaries identified to have dementia and medication dispensation data recorded between 1 April 2010, or cohort entry and 31 March 2015. Anticholinergic medications from the anticholinergic cognitive burden scale (ACB) were abstracted. A look back period of 365 days identified if a PPI had been dispensed preceding anticholinergic dispensation. PPI initiation within 30, 60, 90, or 180 days of the anticholinergic medication was assessed. Demographic description of those dispensed anticholinergic medications or PPIs were reported. Risk factors for the prescribing cascade were investigated with logistic regression and Cox proportional hazards modelling including a sex-stratified analysis.

Results: We identified 28,952 Nova Scotia Seniors' Pharmacare beneficiaries with dementia and prescription dispensation data. Anticholinergic medications were frequently dispensed with 63.4% of the cohort dispensed at least one prescription for an anticholinergic medication. The prescribing cascade defined as up to 180-days between anticholinergic medication inititation and PPI dispensation, occurred in 1,845 Nova Scotia Seniors' Pharmacare beneficiaries with dementia (incidence 6.4%). Multivariate regression showed those experiencing the prescribing cascade after initiating any anticholinergic were younger (OR 0.98, 95%CI [0.97–0.98]), less likely to live in an urban location (OR 0.82, 95%CI [0.74–0.91]), or to be men (OR 0.74, 95%CI [0.67–0.82]). Cox regression demonstrated an increased risk of starting a PPI within 180 days when initiating any medication from the ACB (HR 1.38, 95%CI [1.29–1.58]).

Discussion: Regression modelling suggested that anticholinergic medications increased the risk of PPI dispensation consistent with a prescribing cascade in the cohort. The identification of the prescribing cascade in this population of older Nova Scotia Seniors' Pharmacare Program beneficiaries with dementia using administrative health data highlights how routinely collected health data can be used to identify prescribing cascades.

Keywords: prescribing cascade, prescribing cascades, anticholinergic activity, proton pump inhibitor, dementia, prescribing quality, inappropriate medication, inappropriate medication prescriptions

INTRODUCTION

The concept of the prescribing cascade was first reported by Rochon and Gurwitz in 1995 (Rochon and Gurwitz, 1995).

The prescribing cascade was defined as existing when an adverse drug event (ADE) was misinterpreted as a new medical condition that resulted in a new medication being prescribed to treat the ADE (Rochon and Gurwitz, 1995; Rochon and Gurwitz, 2017; McCarthy et al., 2019). Prescribing cascades can affect people of any age (Gill et al., 2005; Vouri et al., 2018; Huh et al., 2019; Vouri et al., 2020) but have been found to occur more frequently in older adults (Rochon and Gurwitz, 2017; McCarthy et al., 2019). This is due in part to increased polypharmacy among older compared to younger adults which increases exposure to drugs that potentially initiate the prescribing cascade (Beijer and de Blaey, 2002; Canadian Institute for Health Information, 2018). Older adults with dementia are even more susceptible to ADE than similarly aged controls without dementia as they often are prescribed an even greater number of medications (Kanagaratnam et al., 2017; Mullan et al., 2019). Prescribing cascades are an important public health issue. ADEs and inappropriate medication use can contribute to significant financial and health-related quality of life costs both of which affect health care systems and individuals (D'hulster et al., 2022; Mekonnen et al., 2021; Malakouti et al., 2021). Therefore, it is important from both clinical and policy perspectives to begin understanding how to prevent, detect, and reverse prescribing cascades (Brath et al., 2018).

As an example of a potentially relevant prescribing cascade which has yet to be thoroughly investigated, it has been proposed that older adults prescribed an increased anticholinergic burden were more likely to be prescribed a proton pump inhibitor (PPI) (Rababa et al., 2016). PPIs are the second most prescribed medication for older adults in Canada (Canadian Institute for Health Information, 2018) being used to treat a variety of stomach acid-related pathologies (Ahmed and Clarke, 2022). This high level of use raises concerns for overuse (Forgacs and Loganayagam, 2008; Farrell et al., 2017). In 2016, the Canadian Institute for Health Information reported that 23.6% of older adults using PPIs might have been using them inappropriately (Canadian Institute for Health Information, 2018). Concerns regarding overuse make PPIs a common target for deprescribing (the process of withdrawal of an inappropriate medication, supervised by a health care professional to manage polypharmacy and improve outcomes (Reeve et al., 2015)). PPI deprescribing is recommended in many cases after more than 8 weeks of therapy (Boghossian et al., 2017; Farrell et al., 2017; Williams et al., 2019; Deprescribing.org, 2022). Discontinuation of PPIs is recommended due to their association with increased risk of pneumonia (Lin et al., 2019; Marchina et al., 2019; Wang et al., 2019; Wongtrakul et al., 2020), deleterious effect on the gut microbiome (Minalyan et al., 2017; Kuo et al., 2021; Tsujimoto et al., 2021; Okuyama et al., 2022), poor outcome after COVID-19 infection (Yozgat et al., 2021; Ramachandran et al., 2022), fracture (Park et al., 2020; Veettil et al., 2022), *Clostridium difficile* infections (Kuo et al., 2021), and death (Brown et al., 2021; Aby et al., 2022).

Anticholinergic medication refers to a broad and diverse classification of medications (Nishtala et al., 2016; Villalba-Moreno et al., 2016) that includes, for example, antihistamines, antidepressants, and bladder anticholinergics. Anticholinergic medications antagonize the muscarinic receptors (subtypes 1 through 5) which are distributed throughout the body. Many medications have anticholinergic activity without the muscarinic receptor as the intended target receptor. The level of antagonistic activity varies between agents and can be measured using a variety of scales to quantify or rank the anticholinergic activity of medications with this property. There are many scales that quantify the anticholinergic activity of medications (Salahudeen et al., 2015; Al Rihani et al., 2021). The Anticholinergic Cognitive Burden (ACB) scale describes anticholinergic activity on a 4-point scale, with higher scores indicating stronger activity, and increased likelihood of ADE (Boustani et al., 2008). The ACB was chosen as it is a North American scale that was easily applied in the setting, offered a simple description of the anticholinergic activity as strong, moderate, or weak, and was freely available for use when the study was planned. Classical anticholinergic ADEs include dry mouth, decreased lower esophageal sphincter tone, urinary retention and constipation among others (Rudolph et al., 2008). More concerning for older adults is that anticholinergic medication exposure has been associated with an increased risk of falls (Ek et al., 2019; Shmuel et al., 2021), delirium (Oudewortel et al., 2021; Welk et al., 2022), dementia (Zheng et al., 2021) and poorer outcomes in those with dementia (Bishara et al., 2021; Oudewortel et al., 2021). This has led to recommendations for older adults to avoid anticholinergic medications but as this represents such a diverse group of medications it is challenging for prescribers to recognize these agents or even know which alternatives exist.

Rababa et al. proposed a novel prescribing cascade whereby anticholinergic induced gastrointestinal ADE were misinterpreted as new symptoms of gastroesophageal reflux and PPI prescription would follow. This was tested and

identified in a cohort of older adults living in a long-term care home (Rababa et al., 2016), however it has not been more broadly investigated. Older adults living with dementia may have an impaired ability to explain their symptoms or perhaps recount with clarity when gastrointestinal symptoms begin, making it exceedingly challenging for clinicians to recognize the potential prescribing cascade of anticholinergic induced gastrointestinal ADE thereupon being treated with a PPI. The prescribing cascade of anticholinergic medication exposures in older adults with dementia leading to PPI prescription is the focus of the present study. The hypothesis to be explored is that there is increased prescribing of PPIs temporally associated with initiation of a strongly anticholinergic medication. Our objective was to determine if there is an association between anticholinergic medication initiation and PPI prescribing consistent with a prescribing cascade in older adults with dementia.

MATERIALS AND METHODS

Data Description

Health Data Nova Scotia (HDNS) provided linked administrative claims data extracted from provincial data sources including Medical Services Insurance Physician's Billings (MED), Seniors' Pharmacare (PHARM), Vital Statistics (VITAL), and the Canadian Institute for Health Information—Discharge Abstract Database (DAD). The MED provided details of medically required hospital visits for medical, dental, and optometric services with some restrictions for eligible residents. The DAD captured administrative, clinical, and demographic information on hospital discharges in Canada. The PHARM database catalogued dispensing data for Nova Scotia Seniors' Pharmacare beneficiaries. Nova Scotia Seniors' Pharmacare is a voluntary provincial drug insurance program that covers a formulary of prescription medications and is available to adults over 65 years of age in Nova Scotia. VITAL database provided the date of death for censoring.

Cohort entry was assigned when an eligible Nova Scotia Seniors' Pharmacare beneficiary was identified to have had any one of the International Classification of Diseases Clinical Modification (ICD) 9/10 codes that identify dementia from the MED or DAD databases within the date range of 1 March 2005, to 31 March 2015, to create the most complete cohort of older adults with dementia in the province as possible. The particular ICD 9/10 codes used to define dementia were previously identified by the Nova Scotia Dementia Strategy (Dementia Strategy, 2021) (**Supplementary Table S1**). At cohort entry, data collection included the sex of the subject, first date of dementia diagnosis identified in the observation period, and the geographic location of residence specified by the second digit of the postal code whereby 0 represents a rural location and digits 1–9 represent urban sites (Nova Scotia, 2022). Once meeting cohort entry criteria, prescription drug dispensation data for anticholinergic medications according to the ACB scale (Boustani et al., 2008) was collected over the five-year period from 1 April 2010, to 31 March 2015. The PHARM database provided PPI dispensation data from cohort entry or 1 April 2009, to 31 March 2015, which allowed a look-back period of 1 year to test that PPI dispensation followed the anticholinergic medications. A 1-year look-back period was considered adequate to allow for the a new PPI prescription to be related to a new indication and the likelihood that a PPI was needed again due to an underlying medical condition would be similar in both those initiating anticholinergics and those not on an anticholinergic. Exposure to a medication was defined as any dispensation according to the PHARM record, with the required assumption that dispensation was equivalent to medication use. The PHARM data included medication name, quantity dispensed, days supplied, and prescription fill date. Cohort exit was at the date of death or study end date of 31 March 2015. **Figure 1** shows the flow of patient subjects through the analytic procedures for reference.

Analytic Procedure

From 1 April 2010, or cohort entry which could occur up until 31 March 2015, details of medication dispensation for anticholinergic medications were abstracted from the PHARM database, including details of the strength of the anticholinergic according to the ACB scale (Boustani et al., 2008). A look-back period of 365 days from the first date of dispensation of an anticholinergic medication from the ACB scale was used to identify if a PPI had been dispensed in the year preceding the first recorded anticholinergic dispensation. Once confirmed that a PPI did not precede the anticholinergic medication, a forward look in time appraised for PPI initiation within 30, 60, 90, or 180 days of the anticholinergic medication. A stratified analysis was then repeated, categorizing by strength (strong, moderate, and weak) of anticholinergic medications according to the ACB scale. Patient characteristics of those experiencing the prescribing cascade were explored using descriptive statistics. Logistic regression (crude and adjusted) was used to identify risk factors for the prescribing cascade (sex, age at dementia diagnosis, rural or urban location of residence). We then used a Cox proportional hazards model to explore being dispensed a PPI as the outcome of interest in a survival analysis. This method allowed comparison of those who were prescribed a PPI and those who did and did not receive an anticholinergic medication prior to PPI initiation. Time to event was considered from the date of the anticholinergic medication prescription to the dispensing of the PPI, with comparisons made for those dispensed and not dispensed an anticholinergic medication with censoring at 180 days. Missing data were handled using case-wise deletion.

Statistical Software

All data analyses were completed on STATA version 15.1, StataCorp, Lakeway Drive, College Station, Texas, United States.

RESULTS

In the period from 1 April 2005, to 31 March 2015, there were 28,952 (17,946 women (62.0%) and 10,528 men (36.4%)) Nova Scotia Seniors' Pharmacare beneficiaries identified to have a dementia diagnosis. The average age at dementia diagnosis

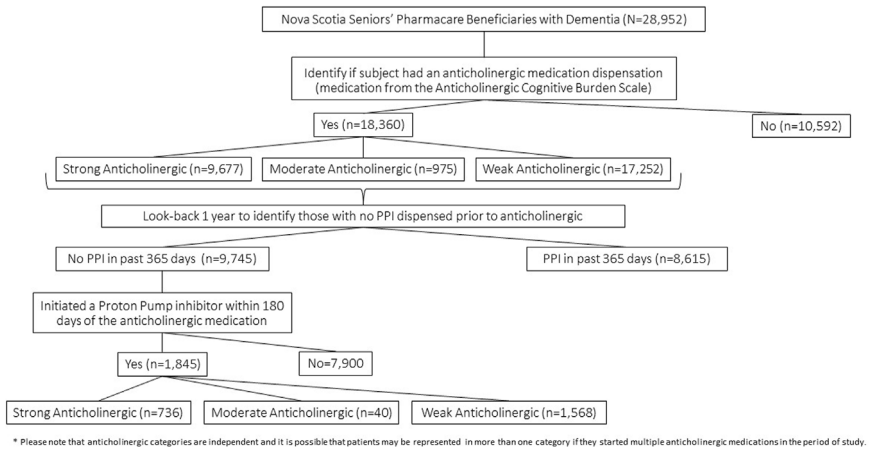


FIGURE 1 | Patient flow through study analytic procedure.

TABLE 1 | Anticholinergic and Proton Pump Inhibitor (PPI) Dispensation including Prescribing Cascade Occurrence in the cohort of older adults with dementia.

Subjects (n = 28,952)	Any anticholinergic	Anticholinergic level 3 (strong)	Anticholinergic level 2 (Moderate)	Anticholinergic level 1 (weak)	PPI
Number of subjects with at least one dispensation, n	18,360	9,677	975	17,252	10,559
Age at diagnosis mean (standard deviation)	81.1 (7.9)	80.6 (7.9)	78.6 (8.3)	81.2 (7.9)	80.9 (7.9)
Female sex n (%)	12,411 (68.5)	6,760 (70.7)	614 (63.9)	11,670 (68.5)	7,078 (68.1)
Rural location of residence, n (%)	6,407 (34.9)	3,433 (35.5)	340 (34.9)	5,990 (34.7)	3,789 (35.9)
Prescribing cascade PPI prescribed within 180 days	1,845	736	40	1,568	—
Women n (%)	1,230 (66.7%)	523 (71.0%)	19 (47.5%)	1,027 (65.5%)	—
Prescribing cascade within 90 days	1,417	544	26	1,178	—
Women n (%)	969 (68.4%)	397 (73.0%)	11 (42.3%)	788 (66.9%)	—
Prescribing cascade within 60 days	1,174	457	22	958	—
Women n (%)	810 (69.0%)	339 (74.1%)	8 (36.4%)	644 (67.2%)	—
Prescribing cascade within 30 days	780	306	15	637	—
Women n (%)	549 (70.4%)	232 (75.8%)	<5	440 (69.1)	—

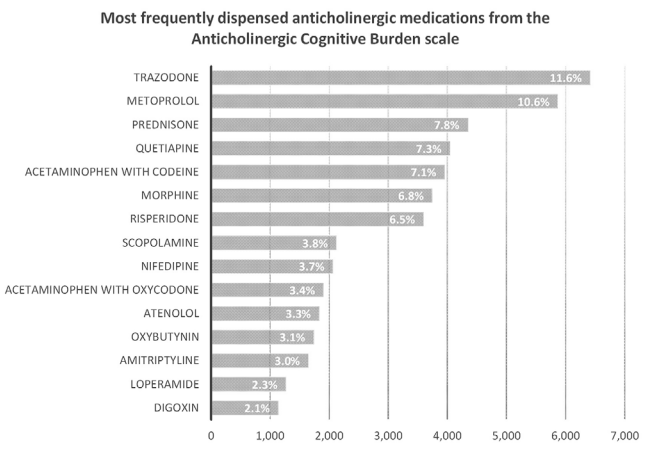


FIGURE 2 | Number and percent of Nova Scotia Senior's Pharmacare Beneficiaries with dementia dispensed at least one medication from the Anticholinergic Cognitive Burden scale for the top fifyeen most frequently dispensed medications.

was 81.1 years (95% CI: 81.0–81.2) with women being slightly older than men [mean 82.1 years (95% CI: 82.0–82.2) compared to 79.6 years (95% CI: 79.4–79.7) ($p < 0.00001$)]. At cohort entry 32.3% of the cohort resided in a rural location. The mean duration of follow-up in the cohort was 3.6 years.

We describe the number of Nova Scotia Seniors' Pharmacare Beneficiaries with dementia dispensed at least one anticholinergic medication or PPI between 1 April 2010, and 31 March 2015, in **Table 1**. The most frequently dispensed anticholinergic medications are summarized in **Figure 2**; a detailed list of the anticholinergic medications dispensed is presented in **Appendix Table A1**. More than 75% of those dispensed any anticholinergic medication were dispensed more than one over the period of study. The average number of anticholinergic medications dispensed to those receiving least one medication from the ACB scale was 3 (range 1–14). PPIs dispensed included: rabeprazole (n = 4,539, 50.4%), omeprazole (n = 2,552, 27.8%), pantoprazole (n = 1,823, 20.0%), lansoprazole (n = 148, 1.7%) and esomeprazole (n = 10, 0.1%).

We identified 1,845 cases where older adults with dementia initiated a PPI within 6 months (180 days) of starting an anticholinergic medication (**Table 1**). Examining the strength of the anticholinergic medications according to the ACB scale shows that most medications were in the strong and weak categories with dispensations to women predominating in both of those categories. However, men who met the criteria for the prescribing cascade were more commonly dispensed medications in the moderate activity category prior to PPI initiation. An exploration of the robustness of the prescribing cascade association by reducing the interval from 180 to 90, 60, and 30 days is displayed in **Table 1**. More than 50% of the identified cases of the prescribing cascade occurred within 60 days of the anticholinergic medication prescription being dispensed.

Multivariate regression (**Table 2**) showed those experiencing the prescribing cascade after initiating any anticholinergic (initiated a PPI 1–180 days of an anticholinergic medication) were younger (OR 0.98, 95%CI: 0.97–0.98), less likely to live in an urban location (OR 0.82, 95%CI: 0.74–0.91), and less likely to be men (OR 0.74, 95%CI: 0.67–0.82). Crude estimates were similar for age (OR 0.98, 95%CI: 0.97–0.98), rurality (OR 0.77, 95%CI: 0.70–0.85), and the effect of sex (OR 0.79, 95%CI: 0.71–0.87). Analyses limited to strong anticholinergic medications showed similar trends with age, with younger adults (OR 0.96, 95%CI: 0.95–0.97) and those living in a rural location (OR 0.86, 95%CI: 0.73–0.99) being more likely to experience a prescribing cascade, although the association with sex was not maintained (OR 0.58, 95%CI: 0.3–1.46). Analyses limited to moderate anticholinergic medications showed similar trends with age (OR 0.91, 95%CI: 0.87–0.95), whereas rurality (OR 1.04, 95%CI: 0.53–2.02) and sex (OR 1.47, 95%CI: 0.79–44.8) failed to show statistically significant associations. Use of weak anticholinergic medications showed similar trends as overall with younger age (OR 0.98, 95%CI: 0.97–0.98), those living in a rural location (OR 0.83, 95%CI: 0.75–0.92), and women (OR 0.79, 95%CI: 0.71–0.88) being associated with increased odds of meeting the criteria of the prescribing cascade.

Cox regression (**Table 3**) demonstrated an increased risk of starting a PPI within 180 days of initiating an anticholinergic from the ACB scale (HR 1.38, 95%CI: 1.29–1.58), and an even greater risk for those dispensed a strong anticholinergic (HR 6.57, 95%CI: 5.45–7.97), but not a moderate anticholinergic (HR 1.63, 95%CI: 0.68–3.88). There was an increased risk of the prescribing cascade for those dispensed a weak anticholinergic (HR 1.38, 95% CI: 1.25–1.82) but much less of an association than identified for the stronger agents, consistent with the hypothesis. In a sex-stratified analyses, the prescribing cascade was identified to exist in men with a significantly increased risk for PPI after anticholinergic medication (HR 1.27 95%CI: 1.06–1.53) and even more so for women (HR 1.43 95%CI: 1.29–1.66).

DISCUSSION

We found evidence for a prescribing cascade of anticholinergic medications leading to PPI prescription in this cohort of older adults living with dementia. Both anticholinergic medications and PPIs were frequently dispensed; PPIs were dispensed to more than 25% of the cohort. Weak anticholinergic medications and strong anticholinergic medications were the most frequently dispensed. Overall, 63.4% of the cohort were dispensed at least one prescription for an anticholinergic medication despite these being potentially harmful for this vulnerable population. We found 1,845 instances of the prescribing cascade, as defined by up to a 180-days interval between anticholinergic medication and PPI dispensation among the 28,952 older adults with dementia included in the cohort (incidence 6.4%). The logistic regression and stratified Cox regression results suggest that this prescribing cascade was most common in older women with dementia.

PPIs are commonly prescribed and their use has increased since 2014 with monthly prescription prevalence estimated at 11,000 per 100,000 persons in the United Kingdom Clinical Practice Research Datalink in 2018 (Abrahami et al., 2021). This level of PPI use from the United Kingdom Clinical Practice Research Datalink is much lower than the rate of use in our cohort of older adults with dementia, which we estimate to be at 40,223 per 100,000 persons in the final month of analysis (March 2015 had 3,711 PPI prescriptions written to the cohort sized at 9,226 in that month of observation). This may reflect that our selected population is older, living with more comorbidities, and therefore more likely to be prescribed gastro-protection with a PPI.

Anticholinergic medications from the ACB scale were dispensed to 63.4% of the cohort, reflecting high levels of use. This is concerning given the known risks of anticholinergic medication exposure to older adults with dementia in worsening cognitive outcomes, causing delirium, falls and increasing the risk of dementia (Bishara et al., 2021). Weak anticholinergic medications were the most commonly dispensed, most likely as this group includes many common medications for managing chronic conditions (e.g., metoprolol and warfarin) and reflects medication choices that may be harder to discontinue, switch to other agents and potentially will be lowest risk of cause ADE. Quite concerning are high rates of trazodone, quetiapine, risperidone, and amitriptyline dispensation (**Supplementary Table S1**). These medications are highly anticholinergic, deliriogenic and likely to have an unfavourable risk benefit profile for older adults with dementia. These represent four medications that within our jurisdiction were frequently prescribed and rather than targeting PPI dispensation suggests that actually targeting the frequent prescribing of anticholinergic medications is of a greater importance for improved prescribing.

The identification of the anticholinergic-PPI prescribing cascade in this population of older Nova Scotia Seniors' Pharmacare Program beneficiaries with dementia using administrative health data highlights how routinely collected health data can be used to identify and investigate prescribing cascades. It is important to consider that the prescribing cascade as related to a medication with anticholinergic activity precipitating prescription of a PPI may not always be inappropriate. It is possible that the prescribing cascade identified may reflect an appropriate prescribing decision such

TABLE 2 | Multivariate regression findings for relationships between the prescribing cascade and potential risk factors.

Covariates	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95%CI)
Any Anticholinergic		
Age	0.98 (0.97–0.98)	0.98 (0.97–0.98)
Urban	0.77 (0.70–0.85)	0.82 (0.74–0.91)
Male Sex	0.79 (0.71–0.87)	0.74 (0.67–0.82)
Strong Anticholinergic		
Age	0.96 (0.95–0.97)	0.96 (0.95–0.97)
Urban	0.80 (0.69–0.93)	0.86 (0.73–0.99)
Male Sex	0.64 (0.54–0.75)	0.58 (0.30–1.46)
Moderate Anticholinergic		
Age	0.91 (0.87–0.94)	0.91 (0.87–0.95)
Urban	0.93 (0.48–1.81)	1.04 (0.53–2.02)
Male Sex	1.85 (0.99–3.44)	1.47 (0.79–44.8)
Weak Anticholinergic		
Age	0.98 (0.97–0.99)	0.98 (0.97–0.98)
Urban	0.78 (0.70–0.86)	0.83 (0.75–0.92)
Male Sex	0.84 (0.75–0.93)	0.79 (0.71–0.88)

TABLE 3 | Cox regression results for likelihood of initiating a PPI within 180 days of an anticholinergic medication from the Anticholinergic Cognitive Burden Scale.

Anticholinergic medication category	Unadjusted hazard ratio (95% CI)
Any Anticholinergic	1.38 (1.29–1.58)
Strong Anticholinergic	6.57 (5.45–7.97)
Moderate Anticholinergic	1.63 (0.68–3.88)
Weak Anticholinergic	1.38 (1.25–1.82)

as initiating a PPI as gastroprotection after initiating a selective serotonin reuptake inhibitor or prednisone. Even with the possibility of some prescribing cascades being appropriate the methodology used in this study identifies a mechanism by which theoretical prescribing cascades could be examined using administrative health data. Once identified the information could be used to target a reduction in inappropriate prescribing after communication to prescribers or to develop interventions to address possible inappropriate prescribing.

How to address this prescribing cascade or others like it and reduce its risk of occurrence will also take effort from prescribers and collaboration from all members of the healthcare team. An Ontario-based qualitative study investigated the patient and provider perspectives on prescribing cascades in community-dwelling adults aged 65 and older (Farrell et al., 2020). Using semi-structured interviews with patients, pharmacists, and physicians evolving themes were identified in consideration of best ways to resolve prescribing cascades. The three main themes were lack of awareness of the prescribing cascade, uncertainty regarding provider/patient accountability, and lack of available information or ability to collaborate. In recognizing these themes, the authors indicated nine actions some of which include patient empowerment, increasing the role for pharmacists to facilitate prescribing and monitoring, using alerts in prescribing and dispensing software, and incorporation of current prescribing pitfalls and prescribing cascades into medical education. These actions can further be condensed to prevention, detection, and reversal. The implementation of these strategies will be better executed with a cohesive, collaborative strategy supported by health structures including healthcare providers and regular assessment of administrative health data.

A commonly asked question is how harmful prescribing cascades can be reversed. Exploring the themes identified by Farrell et al. a scoping review focusing on the prevention, detection, and reversal of prescribing cascades (Brath et al., 2018) showed that successful strategies for prevention include patient education and empowerment and providing providers with a list of cascades with additional guidance to start with low doses of medications when prescribing cascade implicated medications must be used. In general, principles that support deprescribing also support detection and avoidance of prescribing cascades. Primary care practices have found success in identifying potentially inappropriate medication use when a pharmacist was integrated into interprofessional care teams. For example, a study from Quebec, Canada assessed the impact of pharmacists integrated into Family Medicine Groups. Within the Family Medicine Groups pharmacists performed medication reviews that detected 300 drug related problems (an average of 7.2 per patient), with the most common being 'drug use without indication' (27%) (Khaira et al., 2020). Unfortunately to date, there is not a robust healthcare system-entrenched method for supporting patients in deprescribing. Pharmacists have the skills to support deprescribing but may lack access to essential personal health information and an effective means of providing collaborative and coordinated deprescribing services.

Limitations

Our study is not without limitations. As our analyses were based on administrative data, we lacked the ability to assess clinical factors or indications that entered the prescribing decisions. Additionally, we relied on dispensation data which does not provide details as to whether medications were taken as prescribed, or if taken how successfully prescription directions were adhered to. We did not have access to details of over-the-counter medications some of which are anticholinergic (e.g., antihistamines and muscle relaxers). We also do not know if non-prescription PPIs were self-selected and used rather than obtaining a prescription PPI. Our population of Nova Scotia Seniors' Pharmacare beneficiaries covers about 63% of adults 65 years of age and older in Nova Scotia. Nova Scotia Seniors' Pharmacare beneficiaries include those who have enrolled in the voluntary insurance program and is less likely to include those with private insurance that continues after retirement and those who do not wish to pay for medication insurance due to perception of low need, low income, or low literacy.

CONCLUSION

The use of highly anticholinergic medications in older adults who live with dementia is a concern due to the adverse events associated with their use. Identification of the prescribing cascade associated with anticholinergic medications leading to

PPI prescription in older adults living with dementia is only one component of the potential solution. Avoiding prescription of potently anticholinergic medications or having pharmacists act on alerts when strongly anticholinergic medications are prescribed is likely to be most successful for reducing complications associated with anticholinergic medication use like the prescribing cascade described. If anticholinergic medications are prescribed avoiding a prescribing cascade will require empowerment of patients or care providers by providing them with the tools and education to identify adverse events, consistent messaging and follow up to evaluate tolerance and potential ADE when new medications are started. Success in prescribing cascade management will likely only be achieved when methods for interdisciplinary communication and interventions are created and supported by health data evaluation and structured cross-discipline communication. Some of these ideals may be realized when we determine how to share e-health records among providers to allow for seamless transfer of care between providers, expansion of drug utilization evaluation and routine assessment of prescribing indicators to capture prescribing trends with increased use of prescribing alerts to warn when a potential prescribing cascade is identified. Ideally, legislation or practice agreements would support these measures and provide a framework for collaboration to the outcome of improved prescribing.

DATA AVAILABILITY STATEMENT

The raw data will be made available upon reasonable request once approved by the Research Ethics board and data custodian HDNS.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Nova Scotia Health Research Ethics Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ST conceived the study, completed the protocol, completed analysis, drafted the manuscript and collated revisions. AH worked through some data interpretation, worked on introduction and discussion and worked on designing appendices/tables. SB, SK, and MA provided oversight and support for all aspects of the project and added revisions and editing at each stage. All authors have approved the paper as submitted.

FUNDING

This work is supported by the CSHP Foundation and the Canadian Consortium on Neurodegeneration in Aging (CCNA) under Team 14 (PI: Melissa Andrew), which investigates how multi-morbidity modifies the risk of dementia and the patterns of disease expression. The CCNA receives funding from the Canadian Institutes of Health Research (CNA-137794) and partner organizations (www.ccna-ccnv.ca).

ACKNOWLEDGMENTS

The data used in this report were made available by Health Data Nova Scotia of Dalhousie University. Although this research is based on data obtained from the Nova Scotia Department of Health and Wellness, the observations and opinions expressed are those of the authors and do not represent those of either Health Data Nova Scotia or the Department of Health and Wellness.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.878092/full#supplementary-material

REFERENCES

Abrahami, D., McDonald, E. G., Schnitzer, M., and Azoulay, L. (2021). Trends in Prescribing Patterns of Proton Pump Inhibitors Surrounding New Guidelines. *Ann. Epidemiol.* 55, 24–26. doi:10.1016/j.annepidem.2020.12.002

Aby, E. S., Tappata, M., Rodin, H., and Debes, J. D. (2022). Assessment of Proton-Pump Inhibitor Use, Race, Socioeconomic Status, and Mortality in Individuals with COVID-19. *Eur. J. Gastroenterol. Hepatol.* 34 (2), 239. doi:10.1097/MEG.0000000000002138

Ahmed, A., and Clarke, J. O. (2022). "Proton Pump Inhibitors (PPI),". [Internet] in *StatPearls* (Treasure Island (FL): StatPearls Publishing). Available from: http://www.ncbi.nlm.nih.gov/books/NBK557385/.

Al Rihani, S. B., Deodhar, M., Darakjian, L. I., Dow, P., Smith, M. K., Bikmetov, R., et al. (2021). Quantifying Anticholinergic Burden and Sedative Load in Older Adults with Polypharmacy: A Systematic Review of Risk Scales and Models. *Drugs Aging* 38 (11), 977–994. doi:10.1007/s40266-021-00895-x

Beijer, H. J., and de Blaey, C. J. (2002). Hospitalisations Caused by Adverse Drug Reactions (ADR): a Meta-Analysis of Observational Studies. *Pharm. World Sci.* 24 (2), 46–54. doi:10.1023/a:1015570104121

Bishara, D., Perera, G., Harwood, D., Taylor, D., Sauer, J., Funnell, N., et al. (2021). Centrally Acting Anticholinergic Drugs Used for Urinary Conditions Associated with Worse Outcomes in Dementia. *J. Am. Med. Dir. Assoc.* 22 (12), 2547–2552. doi:10.1016/j.jamda.2021.08.011

Boghossian, T. A., Rashid, F. J., Thompson, W., Welch, V., Moayyedi, P., Rojas-Fernandez, C., et al. (2017). Deprescribing versus Continuation of Chronic Proton Pump Inhibitor Use in Adults. *Cochrane Database Syst. Rev.* 3, CD011969. doi:10.1002/14651858.CD011969.pub2

Boustani, M., Campbell, N., Munger, S., Maidment, I., and Fox, C. (2008). Impact of Anticholinergics on the Aging Brain: a Review and Practical Application. *Aging Health* 4 (3), 311–320. doi:10.2217/1745509x.4.3.311

Brath, H., Mehta, N., Savage, R. D., Gill, S. S., Wu, W., Bronskill, S. E., et al. (2018). What Is Known about Preventing, Detecting, and Reversing Prescribing Cascades: A Scoping Review. *J. Am. Geriatr. Soc.* 66 (11), 2079–2085. doi:10.1111/jgs.15543

Brown, J. P., Tazare, J. R., Williamson, E., Mansfield, K. E., Evans, S. J., Tomlinson, L. A., et al. (2021). Proton Pump Inhibitors and Risk of All-Cause and Cause-specific Mortality: A Cohort Study. *Br. J. Clin. Pharmacol.* 87 (8), 3150–3161. doi:10.1111/bcp.14728

Canadian Institute for Health Information (2018). *Drug Use Among Seniors in Canada*. Ottawa, ON: CIHI.

Dementia Strategy (2021). Dementia Strategy | novascotia.Ca. Available from: https://novascotia.ca/dhw/dementia/.

Deprescribing.org (2022). Deprescribing Guidelines and Algorithms. Available from: https://deprescribing.org/resources/deprescribing-guidelines-algorithms/.

D'hulster, E., Quintens, C., Bisschops, R., Willems, R., Peetermans, W. E., Verbakel, J. Y., et al. (2022). Cost-effectiveness of Check of Medication Appropriateness: Methodological Approach. *Int. J. Clin. Pharm.* 44 (2), 399–408. doi:10.1007/s11096-021-01356-6

Ek, S., Rizzuto, D., Fratiglioni, L., Calderón-Larrañaga, A., Johnell, K., Sjöberg, L., et al. (2019). Risk Factors for Injurious Falls in Older Adults: The Role of Sex and Length of Follow-Up. *J. Am. Geriatr. Soc.* 67 (2), 246–253. doi:10.1111/jgs.15657

Farrell, B., Pottie, K., Thompson, W., Boghossian, T., Pizzola, L., Rashid, F. J., et al. (2017). Deprescribing Proton Pump Inhibitors: Evidence-Based Clinical Practice Guideline. *Can. Fam. Physician* 63 (5), 354–364.

Farrell, B. J., Jeffs, L., Irving, H., and McCarthy, L. M. (2020). Patient and Provider Perspectives on the Development and Resolution of Prescribing Cascades: a Qualitative Study. *BMC Geriatr.* 20 (1), 368. doi:10.1186/s12877-020-01774-7

Forgacs, I., and Loganayagam, A. (2008). Overprescribing Proton Pump Inhibitors. *BMJ* 336 (7634), 2–3. doi:10.1136/bmj.39406.449456.BE

Gill, S. S., Mamdani, M., Naglie, G., Streiner, D. L., Bronskill, S. E., Kopp, A., et al. (2005). A Prescribing Cascade Involving Cholinesterase Inhibitors and Anticholinergic Drugs. *Arch. Intern Med.* 165 (7), 808–813. doi:10.1001/archinte.165.7.808

Huh, Y., Kim, D. H., Choi, M., Park, J. H., Kwon, D. Y., Jung, J. H., et al. (2019). Metoclopramide and Levosulpiride Use and Subsequent Levodopa Prescription in the Korean Elderly: The Prescribing Cascade. *J. Clin. Med.* 8 (9). doi:10.3390/jcm8091496

Kanagaratnam, L., Dramé, M., Novella, J. L., Trenque, T., Joachim, C., Nazeyrollas, P., et al. (2017). Risk Factors for Adverse Drug Reactions in Older Subjects Hospitalized in a Dedicated Dementia Unit. *Am. J. Geriatr. Psychiatry* 25 (3), 290–296. doi:10.1016/j.jagp.2016.07.002

Khaira, M., Mathers, A., Benny Gerard, N., and Dolovich, L. (2020). The Evolving Role and Impact of Integrating Pharmacists into Primary Care Teams: Experience from Ontario, Canada. *Pharm. (Basel)* 8 (4), E234. doi:10.3390/pharmacy8040234

Kuo, C. J., Lin, C. Y., Chen, C. W., Hsu, C. Y., Hsieh, S. Y., Chiu, C. T., et al. (2021). Risk of Enteric Infection in Patients with Gastric Acid Supressive Drugs: A Population-Based Case-Control Study. *J. Pers. Med.* 11 (11), 1063. doi:10.3390/jpm11111063

Lin, W. L., Muo, C. S., Lin, W. C., Hsieh, Y. W., and Kao, C. H. (2019). Association of Increased Risk of Pneumonia and Using Proton Pump Inhibitors in Patients with Type II Diabetes Mellitus. *Dose Response* 17 (2), 1559325819843383. doi:10.1177/1559325819843383

Malakouti, S. K., Javan-Noughabi, J., Yousefzadeh, N., Rezapour, A., Mortazavi, S. S., Jahangiri, R., et al. (2021). A Systematic Review of Potentially Inappropriate Medications Use and Related Costs Among the Elderly. *Value Health Reg. Issues* 25, 172–179. doi:10.1016/j.vhri.2021.05.003

Marchina, S., Doros, G., Modak, J., Helenius, J., Aycock, D. M., and Kumar, S. (2019). Acid-suppressive Medications and Risk of Pneumonia in Acute Stroke Patients: A Systematic Review and Meta-Analysis. *J. Neurol. Sci.* 400, 122–128. doi:10.1016/j.jns.2019.02.041

McCarthy, L. M., Visentin, J. D., and Rochon, P. A. (2019). Assessing the Scope and Appropriateness of Prescribing Cascades. *J. Am. Geriatr. Soc.* 67 (5), 1023–1026. doi:10.1111/jgs.15800

Mekonnen, A. B., Redley, B., de Courten, B., and Manias, E. (2021). Potentially Inappropriate Prescribing and its Associations with Health-Related and System-Related Outcomes in Hospitalised Older Adults: A Systematic Review and Meta-Analysis. *Br. J. Clin. Pharmacol.* 87 (11), 4150–4172. doi:10.1111/bcp.14870

Minalyan, A., Gabrielyan, L., Scott, D., Jacobs, J., and Pisegna, J. R. (2017). The Gastric and Intestinal Microbiome: Role of Proton Pump Inhibitors. *Curr. Gastroenterol. Rep.* 19 (8), 42. doi:10.1007/s11894-017-0577-6

Mullan, J., Burns, P., Mohanan, L., Lago, L., Jordan, M., and Potter, J. (2019). Hospitalisation for Medication Misadventures Among Older Adults with and without Dementia: A 5-year Retrospective Study. *Australas. J. Ageing* 38 (4), e135–e141. doi:10.1111/ajag.12712

Nishtala, P. S., Salahudeen, M. S., and Hilmer, S. N. (2016). Anticholinergics: Theoretical and Clinical Overview. *Expert Opin. Drug Saf.* 15 (6), 753–768. doi:10.1517/14740338.2016.1165664

Nova Scotia (2022). Canada Zip Codes. [Internet]. [cited 2022 Jan 16]. Available from: https://worldpostalcode.com/canada/nova-scotia/.

Okuyama, Y., Okamoto, T., Sasaki, D., Ozaki, K., Songee, J., Hatakeyama, S., et al. (2022). The Influence of Gut Microbiome on Progression of Overactive Bladder Symptoms: a Community-Based 3-year Longitudinal Study in Aomori, Japan. *Int. Urol. Nephrol.* 54 (1), 9–16. doi:10.1007/s11255-021-03044-w

Oudewortel, L., van der Roest, H. G., Onder, G., Wijnen, V. J. M., Liperoti, R., Denkinger, M., et al. (2021). The Association of Anticholinergic Drugs and Delirium in Nursing Home Patients with Dementia: Results from the SHELTER Study. *J. Am. Med. Dir. Assoc.* 22 (10), 2087–2092. doi:10.1016/j.jamda.2021.05.039

Park, J. H., Lee, J., Yu, S. Y., Jung, J. H., Han, K., Kim, D. H., et al. (2020). Comparing Proton Pump Inhibitors with Histamin-2 Receptor Blockers Regarding the Risk of Osteoporotic Fractures: a Nested Case-Control Study of More Than 350,000 Korean Patients with GERD and Peptic Ulcer Disease. *BMC Geriatr.* 20 (1), 407. doi:10.1186/s12877-020-01794-3

Rababa, M., Al-Ghassani, A. A., Kovach, C. R., and Dyer, E. M. (2016). Proton Pump Inhibitors and the Prescribing Cascade. *J. Gerontol. Nurs.* 42 (4), 23–3. doi:10.3928/00989134-20151218-04

Ramachandran, P., Perisetti, A., Gajendran, M., Jean-Louis, F., Bansal, P., Dwivedi, A. K., et al. (2022). Pre-hospitalization Proton Pump Inhibitor Use and Clinical Outcomes in COVID-19. *Eur. J. Gastroenterol. Hepatol.* 34 (2), 137–141. doi:10.1097/MEG.0000000000002013

Reeve, E., Gnjidic, D., Long, J., and Hilmer, S. (2015). A Systematic Review of the Emerging Definition of 'deprescribing' with Network Analysis: Implications for Future Research and Clinical Practice. *Br. J. Clin. Pharmacol.* 80 (6), 1254–1268. doi:10.1111/bcp.12732

Rochon, P. A., and Gurwitz, J. H. (1995). Drug Therapy. *Lancet* 346 (8966), 32–36. doi:10.1016/s0140-6736(95)92656-9

Rochon, P. A., and Gurwitz, J. H. (2017). The Prescribing Cascade Revisited. *Lancet* 389 (10081), 1778–1780. doi:10.1016/S0140-6736(17)31188-1

Rudolph, J. L., Salow, M. J., Angelini, M. C., and McGlinchey, R. E. (2008). The Anticholinergic Risk Scale and Anticholinergic Adverse Effects in Older Persons. *Arch. Intern Med.* 168 (5), 508–513. doi:10.1001/archinternmed.2007.106

Salahudeen, M. S., Duffull, S. B., and Nishtala, P. S. (2015). Anticholinergic Burden Quantified by Anticholinergic Risk Scales and Adverse Outcomes in Older People: a Systematic Review. *BMC Geriatr.* 15, 31. doi:10.1186/s12877-015-0029-9

Shmuel, S., Pate, V., Pepin, M. J., Bailey, J. C., Golightly, Y. M., Hanson, L. C., et al. (2021). Effects of Anticholinergic and Sedative Medication Use on Fractures: A Self-Controlled Design Study. *J. Am. Geriatr. Soc.* 69 (11), 3212–3224. doi:10.1111/jgs.17377

Tsujimoto, H., Hirata, Y., Ueda, Y., Kinoshita, N., Tawa, H., Tanaka, Y., et al. (2021). Effect of a Proton-Pump Inhibitor on Intestinal Microbiota in Patients Taking Low-Dose Aspirin. *Eur. J. Clin. Pharmacol.* 77 (11), 1639–1648. doi:10.1007/s00228-021-03167-0

Veettil, S. K., Sadoyu, S., Bald, E. M., Chandran, V. P., Khuu, S. A. T., Pitak, P., et al. (2022). Association of Proton-Pump Inhibitor Use with Adverse Health Outcomes: A Systematic Umbrella Review of Meta-Analyses of Cohort Studies and Randomised Controlled Trials. *Br. J. Clin. Pharmacol.* 88, 1551–1566. doi:10.1111/bcp.15103

Villalba-Moreno, A. M., Alfaro-Lara, E. R., Pérez-Guerrero, M. C., Nieto-Martín, M. D., and Santos-Ramos, B. (2016). Systematic Review on the Use of Anticholinergic Scales in Poly Pathological Patients. *Arch. Gerontol. Geriatr.* 62, 1–8. doi:10.1016/j.archger.2015.10.002

Vouri, S. M., Possinger, M. C., Usmani, S., Solberg, L. M., and Manini, T. (2020). Evaluation of the Potential Acetylcholinesterase Inhibitor-Induced Rhinorrhea Prescribing Cascade. *J. Am. Geriatr. Soc.* 68 (2), 440–441. doi:10.1111/jgs.16224

Vouri, S. M., van Tuyl, J. S., Olsen, M. A., Xian, H., and Schootman, M. (2018). An Evaluation of a Potential Calcium Channel Blocker-Lower-Extremity Edema-Loop Diuretic Prescribing Cascade. *J. Am. Pharm. Assoc. (2003)* 58 (5), 534–539.e4. doi:10.1016/j.japh.2018.06.014

Wang, C. H., Li, C. H., Hsieh, R., Fan, C. Y., Hsu, T. C., Chang, W. C., et al. (2019). Proton Pump Inhibitors Therapy and the Risk of Pneumonia: a Systematic Review and Meta-Analysis of Randomized Controlled Trials and Observational Studies. *Expert Opin. Drug Saf.* 18 (3), 163–172. doi:10.1080/14740338.2019.1577820

Welk, B., Etaby, K., McArthur, E., and Chou, Q. (2022). The Risk of Delirium and Falls or Fractures with the Use of Overactive Bladder Anticholinergic Medications. *Neurourol. Urodyn.* 41 (1), 348–356. doi:10.1002/nau.24827

Williams, S., Miller, G., Khoury, R., and Grossberg, G. T. (2019). Rational Deprescribing in the Elderly. *Ann. Clin. Psychiatry* 31 (2), 144–152.

Wongtrakul, W., Charoenngnam, N., and Ungprasert, P. (2020). Use of Proton Pump Inhibitors Is Associated with a Higher Risk of Pneumonia in Cirrhotic Patients: a Systematic Review and Meta-Analysis. *Ann. Gastroenterol.* 33 (3), 277–284. doi:10.20524/aog.2020.0483

Yozgat, A., Kasapoğlu, B., Can, G., Tanoğlu, A., Sakin, Y. S., Yalçın, K. S., et al. (2021). Long-term Proton Pump Inhibitor Use Is a Risk Factor for Mortality in Patients Hospitalized for COVID-19. *Turk J. Med. Sci.* 51 (3), 1675–1681. doi:10.3906/sag-2103-80

Zheng, Y. B., Shi, L., Zhu, X. M., Bao, Y. P., Bai, L. J., Li, J. Q., et al. (2021). Anticholinergic Drugs and the Risk of Dementia: A Systematic Review and Meta-Analysis. *Neurosci. Biobehav Rev.* 127, 296–306. doi:10.1016/j.neubiorev.2021.04.031

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

APPENDIX 1

TABLE A1 | Anticholinergic Cognitive Burden Scale Medications dispensed to the cohort of Nova Scotia Seniors' Pharmacare Beneficiaries with Dementia.

Anticholinergic medication		Frequency	% of anticholinergic claims
ATC code	**Generic name**		
Anticholinergics_3			
A03AA07	dicycloverine	50	0.09
A04AD01	scopolamine	2,120	3.82
A04AD99	dimenhydrinate	415	0.75
G04BD04	oxybutynin	1,740	3.13
G04BD07	tolterodine	377	0.68
G04BD08	solifenacin	204	0.37
G04BD09	trospium	57	0.10
G04BD10	darifenacin	34	0.06
G04BD11	fesoterodine	31	0.06
M03BC01	orphenadrine (citrate)	6	0.01
N04AA01	trihexyphenidyl	28	0.05
N04AA04	procyclidine	6	0.01
N04AC01	benzatropine	162	0.29
N05AB03	perphenazine	92	0.17
N05AB06	trifluoperazine	52	0.09
N05AH02	clozapine	5	0.01
N05AH03	olanzapine	480	0.86
N05AH04	quetiapine	4,047	7.29
N05BB01	hydroxyzine	152	0.27
N06AA01	desipramine	65	0.27
N06AA02	imipramine	80	0.12
N06AA04	clomipramine	50	0.14
N06AA06	trimipramine	38	0.07
N06AA09	amitriptyline	1,650	2.97
N06AA10	nortriptyline	671	1.21
N06AA12	doxepin	254	0.46
N06AB05	paroxetine	1,053	1.90
Anticholinergics_2			
N02AB02	pethidine	10	0.02
N03AF01	carbamazepine	328	0.59
N04BB01	amantadine	67	0.12
N05AA02	levomepromazine	468	0.84
N05AG02	pimozide	15	0.03
N05AH01	loxapine	123	0.22
Anticholinergics_1			
A02BA01	cimetidine	52	0.09
A07DA03	loperamide	1,271	2.29
B01AC07	dipyridamole	16	0.03
C01AA05	digoxin	1,141	2.06
C01DA08	isosorbide dinitrate	110	0.20
C01DA14	isosorbide mononitrate	274	0.49
C03BA04	chlortalidone	34	0.06
C07AB02	metoprolol	5,869	10.57
C07AB03	atenolol	1,836	3.31
C07CB03	atenolol and other diuretics	76	0.14
C08CA05	Nifedipine	2,063	3.72
C09AA01	captopril	39	0.07
H02AB07	prednisone	4,350	7.84
M04AC01	colchicine	997	1.80
N01AH01	fentanyl	15	0.03
N02AA01	morphine	3,745	6.75
N02AA59	codeine, combinations excl. psycholeptics	3,955	7.12
N02AB03	fentanyl	359	0.65
N02BE51	paracetamol, combinations excl. psycholeptics	1,905	3.43
N05AX08	risperidone	3,598	6.48
N05BA01	diazepam	493	0.89
N05BA05	potassium clorazepate	21	0.04
N05BA12	alprazolam	405	0.73
N06AX05	trazodone	6,418	11.56
N06AX12	bupropion	425	0.77
R03DA04	theophylline	129	0.23
R03DA54	theophylline, combinations excl. psycholeptics	13	0.02
R05DA04	codeine	974	1.75

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership