




Sex differences among users of NSAIDs and opioids during COVID-19 Pandemic

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Abstract

Background Sex-based inequalities in healthcare have been exposed and amplified during the COVID-19 pandemic. However, few studies have reported sex differences in medication utilization and no studies have examined sex differences in prescribed non-steroidal anti-inflammatory drugs (NSAIDs) and opioids utilization.

Aim To compare the utilization patterns of prescribed NSAIDs and opioids between males and females in Manitoba, Canada during the COVID-19 pandemic.

Method A cohort of incident and prevalent users of prescribed NSAIDs and opioids was created. Interrupted times series analysis using autoregressive models were used to evaluate the quarterly change in the prevalent and incident users before and after COVID-19 restrictions were applied (first quarter of 2020).

Results COVID-19 restrictions were associated with a significant decrease in the utilization of prescribed NSAIDs and opioids in all users, followed by a revert to the pre-pandemic trends. Among female prevalent and incident NSAIDs users, there was a significant change in trend after COVID-19 restrictions were introduced ($\beta_3 = 0.087$ and 0.078 , $P = 0.023$ and 0.028 , respectively). However, there was non-significant change in trend among male prevalent and incident NSAIDs and opioids users during the pandemic.

Conclusion In this study, a significant sharp decline in the use of prescribed NSAIDs and opioids was shown in both sexes at the onset of the pandemic. However, a significant upward trend is observed in female NSAIDs users as restrictions began to be lifted.

Keywords COVID-19 pandemic · NSAIDs · Opioids · Sex difference · Utilization

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Impact statements

- Our results suggest that females may have been experiencing the consequences of forgoing their pain medication more frequently compared to males due to COVID-19, highlighting the importance of sex-disaggregated analysis and targeted care for females during stressful conditions.
- Clinicians are being called to incorporate sex and gender considerations into clinical decision-making during pandemics, including pain pharmacotherapy.
- Pharmacists engagement through monitoring patients' drug access post virtual-care visits could substantially improve women's adherence to optimal therapy.
- Incorporating sex-disaggregated results is necessary in advancing pharmacy practice, to ensure equitable, safe

and efficacious therapy for men and women, especially during emergency conditions as pandemics.

Introduction

The COVID-19 pandemic has significantly impacted global health, resulting in over 431 million confirmed cases and more than 5.9 million deaths worldwide, as of February 25, 2022 [1]. However, its impact is not limited to increased morbidity and mortality. Societies and national economies have been disrupted due to public health measures, such as school and business closures [2], which were implemented to slow the rate of infection [3]. In Manitoba for example, a state of emergency was issued on March 20, 2020, restricting public gatherings, enforcing social distancing, and ordering the closure of several non-essential facilities [4]. The healthcare system in Manitoba underwent changes in the way patients accessed essential and non-essential healthcare. Some in-person services were replaced with virtual care, while other services, including non-urgent elective surgeries, were postponed [5, 6].

There is increasing evidence of sex-specific differences in immune responses and inflammatory diseases, indicating that females are more likely to experience chronic pain syndromes than males [7, 8]. Moreover, sex differences in opioid receptors lead to different opioid use disorder risks comparing women to men [9–11]. Such differences have important clinical implications in pain management by healthcare practitioners. NSAIDs and opioids are the most frequently prescribed drugs for pain management [12, 13]. Although evidence shows that women receive more NSAIDs and opioids prescriptions than men, it is unclear how pain relief management differs between different sexes. [12, 13]. Pain is more frequent in women than men, and women have higher susceptibility of developing neuropathic pain and severe postoperative pain in comparison to men [12, 13]. While different social, cultural, and psychological factors play roles in pain reporting, the differential thresholds of pain tolerance and sensitivity between sexes is paramount in investigating pain pharmacotherapy.

Recent studies reported sex differences in related-pandemic pain, especially for females who experience more severe chronic pain than males [14, 15]. It was observed that females faced more challenges during the pandemic, mainly related to gender inequities that affected chronic pain management [14–16].

Global data shows that males are at a higher risk of severe COVID-19 infection and death than females [17], while government measures may disproportionately affect females. For example, in the UK and USA, females reported poorer mental health than males during lockdowns [18, 19]. In one such study, conducted in North York (Ontario, Canada), sex

was not significantly correlated to the number of benzodiazepines dispensed during the pandemic, nor to the likelihood of antidepressant initiation [20]. In another study conducted in British Columbia, Canada, monthly antibiotic prescription rates declined significantly during the pandemic, but rates were comparable for males and females [21].

To date, no study has investigated sex differences in prescribed non-steroidal anti-inflammatory drugs (NSAIDs) and opioids utilization during COVID-19. Opioids and prescribed NSAIDs are the most commonly used drugs for pain management [22], a prevalent condition among Canadian adults, with 1 in 5 adults experiencing chronic pain [23]. Understanding sex differences in prescribed NSAIDs and opioids is crucial, since sex differences may result in differential consequences in morbidity and mortality, as previously suggested on sex/gender roles in opioids prescribing [24].

Aim

The aim of this study is to compare the utilization patterns of prescribed NSAIDs and opioids between males and females in Manitoba, Canada during the COVID-19 pandemic.

Ethics approval

This study has been approved by the University of Manitoba Health Research Ethics Board (HREB #: H2020:335) and access to data was approved by the Health Information Privacy Committee of Manitoba Health in 2020–2021.

Method

Data sources, study design, and population

A retrospective population-based cohort study was conducted using data from the province of Manitoba, Canada. All Manitoba residents who were registered with the provincial health care system and used prescribed NSAIDs or opioids between the July 1 (third quarter), 2016 up till March 31 (first quarter), 2021 were included. No age restrictions were applied, and patients were stratified by sex. Incident users were defined as people who were prescribed NSAIDs or opioids within each quarter with no such drug record in the previous 4 quarters; whereas prevalent users were defined as people who used prescribed NSAIDs or opioids within each quarter. Databases used include the Population Registry (demographic information for all residents of Manitoba, including sex, date of birth) and the drug program information network (DPIN), which contains recorded prescription

data (drug name, and dispensation date by pharmacies in Manitoba regardless of the type of insurance coverage). prescribed NSAIDs and opioids utilization were identified using the Anatomical Therapeutic Chemical (ATC) codes (Supplementary Table 1s).

Statistical analyses

We calculated incidence and prevalence of all prescribed NSAIDs and opioids that were available in the Canadian market in Manitoba during the study period [25–27]. Incidence and prevalence of use were calculated quarterly during the study period and stratified by sex. We report the incidence and prevalence rates, as per 100 Manitoba residents with at least one day of Manitoba health and seniors care (MHSC) coverage at the beginning of the quarter used as the denominator. Interrupted times series analysis using autoregressive models were used to evaluate the quarterly change in the prevalence and incidence of prescribed NSAIDs and opioids use in relation to COVID-19 restrictions [28]. We set the intervention of COVID-19 related restrictions in health-care at the first quarter of 2020. Analyses were conducted using SAS, version 9.4 (SAS Institute, Inc). $P < 0.05$ was used as the threshold for statistical significance.

Results

The quarterly study population ranged from 1,353,485 to 1,411,630 Manitobans, of which 50.23% were females and 49.77% were males. The mean age of the participants was 38 years ($SD = 23.35$) and over 60% were living in urban areas. The most common comorbidities were asthma (26.67%) and hypertension (20.64%). During the study period (Q3-2016 to Q1-2021), there was an overall downward trend in the prevalence of prescribed Rx-NSAIDs and opioids utilization, and a dramatic decline was observed in incident and prevalent users at the onset of COVID-19 restrictions.

Prescribed NSAIDs

Immediately after the implementation of COVID-19 restrictions in Q1-2020, there was a significant decrease of 15.05% ($P = 0.0003$) and 15.94% ($P < 0.0001$) in the percentage change of the prevalence of NSAIDs use in males and females respectively (Fig. 1A).

During the 2nd wave of the COVID-19 pandemic (Q2-2020 to Q1-2021), the trend in the quarterly prevalence of NSAIDs use in males did not significantly change ($\beta_3 = 0.0389$ and $P = 0.2598$), compared to the pre-pandemic

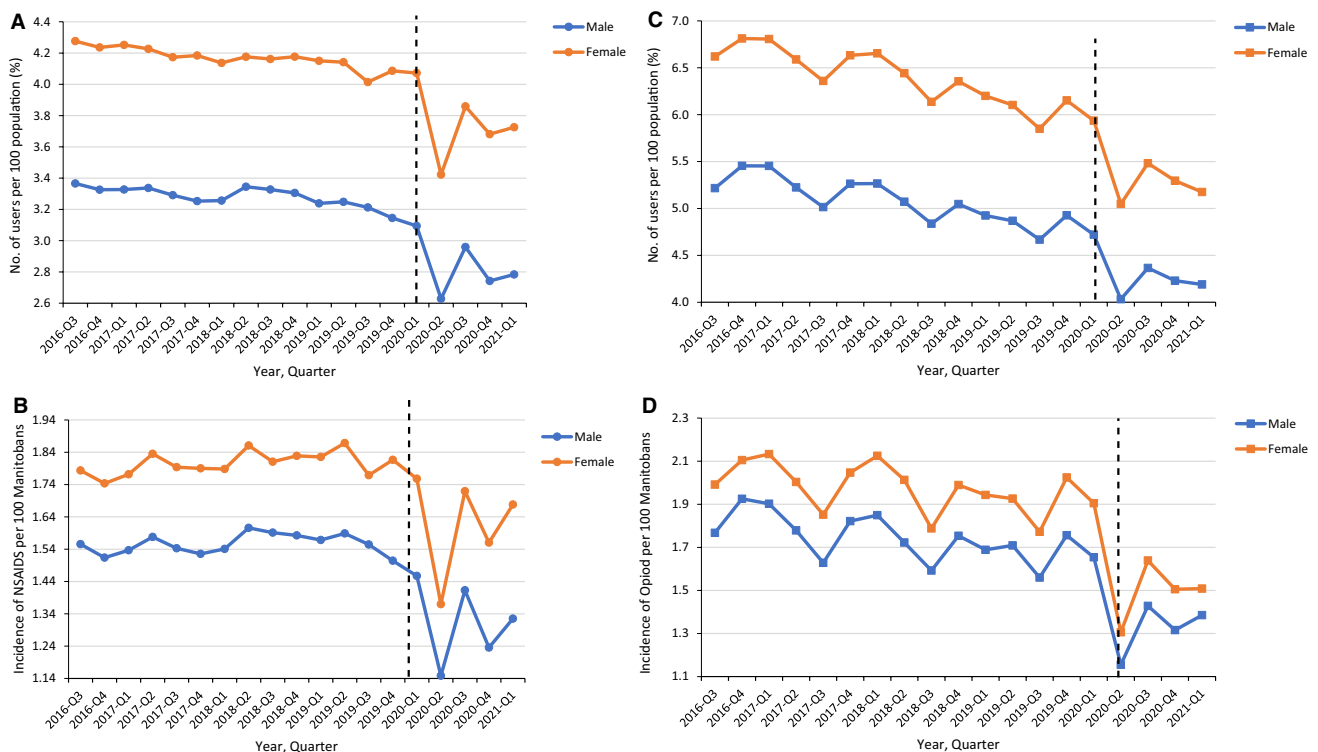


Fig. 1 Prevalence (A) and incidence (B) of NSAID use by sex in Manitoba, Q3-2016–Q1-2021 and the prevalence (C) and incidence (D) of opioid use by sex in Manitoba, Q3-2016–Q1-2021

trend. However, we observed a significant trend change in the quarterly prevalence of NSAIDs use in females during the pandemic ($\beta_3=0.0869$ and $P=0.0232$) compared to the pre-pandemic period.

Following the implementation of COVID-19 restrictions, the incidence of prescribed NSAIDs use in males and females significantly decreased by 21.35% ($P=0.0005$) and 22.17% ($P=0.0001$) respectively (Fig. 1B). During the pandemic, the trend in the quarterly incidence of prescribed NSAIDs use in males did not significantly change ($\beta_3=0.0351$, $P=0.2507$), compared to the pre-pandemic trend. However, we observed a significant trend change in the quarterly incidence of prescribed NSAIDs use in females ($\beta_3=0.0777$, $P=0.0279$) during the pandemic, compared to the pre-pandemic period.

Prescribed opioids

The prevalence of opioid use in males and females significantly decreased with an estimated decrease percentage change of 14.58% ($P=0.0036$) and 14.96% ($P=0.0027$) respectively, immediately after restrictions were applied (Fig. 1C). Furthermore, the trend in the quarterly prevalence of opioids use in males and females during the pandemic did not significantly change ($\beta_3=0.0806$ and 0.0802 , $P=0.2070$ and 0.2798 respectively), compared to the pre-pandemic period.

We also observed a significant decrease of 30.28% ($P=0.0019$) and 31.58% ($P=0.0027$) in the incidence of opioids use in males and females respectively, immediately after restrictions were applied (Fig. 1D). Regarding opioid utilization, the trend in the quarterly incidence of opioids use in males and females during the pandemic did not significantly change ($\beta_3=0.0759$ and 0.0613 , $P=0.1259$ and 0.2956 respectively) compared to the pre-pandemic period.

Discussion

Statement of key findings

Within our cohort of persons prescribed NSAIDs and opioids, we found a significant decrease in the dispensing of these medications at the onset of the pandemic restrictions (during the first quarter of 2020). This dramatic decline was followed by a rise towards the pre-pandemic downward trend in both males and females, but there was no full recovery to the baseline level. However, among female NSAIDs users (prevalent and incident users), there was a sustained effect after COVID-19 restrictions were applied. Among females, we observed a significant upward trend in utilization after restrictions were applied which was significantly different compared to the pre-pandemic trend.

Our findings are consistent with studies in the United States [29–31] and England [31], reporting a decrease in the utilization of NSAIDs and opioids during the pandemic, however in sex aggregated data. Various factors may have influenced the decline in prescribed NSAIDs and opioids at the onset of COVID-19 restrictions. In a pan-Canadian cross-sectional study among adults with chronic pain during the first wave, Lacasse et al. reported the most common reasons attributed to change in pain medication, namely: (1) changes in the pain symptoms, (2) lack of access to clinics and (3) initiating the use of pain medications to compensate the decrease in non-pharmacological management (16). In Manitoba, a transition to virtual care around the same time as restrictions was introduced throughout the province.

Reduced access to prescribed NSAIDs and opioids is concerning since untreated pain can have physical, psychological, and economic consequences, and directly associated with a reduction in the quality of life [32]. New options for virtual care in Manitoba were later announced in April 2020 to improve patient access to physicians [33, 34]. These improved access options might have contributed to the observed rebound effect in NSAIDs and opioids utilization. Our results may also indicate that during the pandemic, people have successfully endured pain without opioids (or used non-prescription NSAIDs), which saved Manitoba's health system precious health care visits in a time of health resource crisis. This assumption requires further investigation as Canada displays high rates of unnecessary opioids use.

A restriction on medication dispensing in Manitoba was introduced on March 19, 2020. Manitoba pharmacists were only permitted to provide a one-month supply for all drug prescriptions, including prescribed NSAIDs and opioids [34]. Moreover, in March 2020, some studies suggested that NSAIDs should be avoided in those with confirmed or suspected COVID-19 as it could increase the severity of the disease [35, 36]. However, recent studies found no associations between NSAIDs use, admission to hospital, and worsened outcomes for patients with COVID-19 [37–43]. Furthermore, we observed a decrease in opioids use among males and females since 2016. This decrease could be attributed to the implementation of opioid stewardship measures across Canada [44].

Interpretation

Our results show that the decline in prescribed NSAIDs and opioids utilization upon the introduction of restrictions was greater in females than males. This reflects a differential impact of restriction measures by sex, where more females may have been experiencing the consequences of forgoing their medication compared to males. This finding is concerning because females tend to be more reliant on NSAIDs

and opioids than males. Females are on average more sensitive to pain and more likely to experience chronic pain than males [8, 45], while some studies have found no sex differences in pain severity [10, 46]. Females are also more likely to be prescribed opioids and NSAIDs [47, 48]. It has also been suggested that the higher prevalence of chronic pain in females might be associated with their increased utilization of NSAIDs and opioids [24]. Remote-work settings and increased household and childcare responsibilities during the pandemic [49] might have affected females' access to prescription medications and could explain the greater decline in utilization observed in females. This study highlighted the importance of sex-disaggregated analysis within the context of COVID-19 impact [7]. Unfortunately, most current medical guidelines are not sex specific [7] and many global health organisations fail to report sex-disaggregated data [50]. Furthermore, female participants are often under-represented in clinical studies [51]. Gender, as an individual's socially constructed role, is also a major determinant of health, influencing how, when, and why a person accesses medical care [7].

Strengths, weaknesses and further research

A major strength of the current study is the province-wide database used which covers the total population of Manitoba, irrespective of their insurance type or socioeconomic class. Furthermore, we used ITS analysis which minimized the impact of measured and unmeasured confounding factors. Limitations of this study should be acknowledged. First, we did not have data on the employment status of participants and the indications/diseases for opioids and prescribed NSAIDs use. Second, our study included sex differences as opposed to sex and gender differences, since gender data are currently unavailable in our databases. Third, our databases record prescription data and not over-the-counter medications nor illicit use, which could underestimate our utilization findings, so further studies are warranted.

Conclusion

COVID-19 pandemic public health restrictions were associated with a significant immediate decline in the utilization of prescribed NSAIDs and opioids among males and females, with a greater decline observed in females. Novel studies on COVID-19 need to address how sex and gender function independently and together to influence health care access and outcomes. Moreover, clinicians are being called to incorporate sex and gender awareness into clinical decision-making. In conclusion, the results of the present study suggest that men and women may differ in the response to lockdown restriction and medications used for

pain relief. Our findings suggest that women may have been experiencing pain more frequently compared to men due to access restrictions. Incorporating sex-disaggregated results is necessary to ensure providing an equitable and effective therapy for all patient groups, especially during emergency conditions as pandemics.

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