BioMedInformatics

MDPI

Article

Cross-National Analysis of Opioid Prescribing Patterns: Enhancements and Insights from the OralOpioids R Package in Canada and the United States

Ankona Banerjee [1,*], Kenneth Nobleza [1], Duc T. Nguyen [1] and Erik Stricker [2]

[1] Center for Epidemiology & Population Health, Baylor College of Medicine, 6620 Main Street, Houston, TX 77030, USA; kenneth.nobleza@bcm.edu (K.N.); duc.nguyen4@bcm.edu (D.T.N.)
[2] Department of Human and Molecular Genetics, Baylor College of Medicine, Houston, TX 77030, USA; erik.stricker@bcm.edu
* Correspondence: ankona.banerjee@bcm.edu

Abstract: Background: The opioid crisis remains a significant public health challenge in North America, highlighted by the substantial need for tools to analyze and understand opioid potency and prescription patterns. **Methods:** The OralOpioids package automates the retrieval, processing, and analysis of opioid data from Health Canada's Drug Product Database (DPD) and the U.S. Food and Drug Administration's (FDA) National Drug Code (NDC) database. It includes functions such as load_Opioid_Table, which integrates country-specific data processing and Morphine Equivalent Dose (MED) calculations, providing a comprehensive dataset for analysis. The package facilitates a comprehensive examination of opioid prescriptions, allowing researchers to identify high-risk opioids and patterns that could inform policy and healthcare practices. **Results:** The integration of MED calculations with Canadian and U.S. data provides a robust tool for assessing opioid potency and prescribing practices. The OralOpioids R package is an essential tool for public health researchers, enabling a detailed analysis of North American opioid prescriptions. **Conclusions:** By providing easy access to opioid potency data and supporting cross-national studies, the package plays a critical role in addressing the opioid crisis. It suggests a model for similar tools that could be adapted for global use, enhancing our capacity to manage and mitigate opioid misuse effectively.

Keywords: R package; opioids; morphine equivalent dose

Citation: Banerjee, A.; Nobleza, K.; Nguyen, D.T.; Stricker, E. Cross-National Analysis of Opioid Prescribing Patterns: Enhancements and Insights from the OralOpioids R Package in Canada and the United States. *BioMedInformatics* **2024**, *4*, 2107–2116. https://doi.org/10.3390/biomedinformatics4030112

Academic Editors: Pentti Nieminen and Alexandre G. De Brevern

Received: 25 June 2024
Revised: 1 September 2024
Accepted: 10 September 2024
Published: 16 September 2024

1. Introduction

The previous study, "OralOpioids: Harnessing R Programming and Data Science to Combat Opioid Misuse", [1] introduced the OralOpioids R package, a pioneering first-of-its-kind tool designed to deepen the understanding of oral prescriptions containing opioids in Canada, a country noted for its significant per-capita consumption of pharmaceutical opioids [1]. This research highlighted the potential of data science in addressing the opioid crisis by providing a comprehensive analysis of opioid prescriptions through Health Canada's Drug Product Database (DPD), revealing patterns that could inform policy and healthcare practices.

Building upon this foundation, the present addendum seeks to extend the scope of our analysis beyond the Canadian context to include the United States, a nation grappling with its own profound opioid epidemic [2]. This extension is motivated by the need to understand opioid misuse within a broader North American framework, recognizing the opioid crisis across borders. By integrating data on U.S. opioids, we aim to uncover comparative insights and potentially shared solutions that can benefit both nations.

The inclusion of U.S. opioid data represents a significant expansion of research capabilities, setting the stage for a detailed cross-national analysis that could unveil critical

dynamics of opioid misuse and inform strategies for intervention at a global level. OralOpioids would be a practical tool for researchers in conducting research on opioid use in both Canada and USA.

Role of Morphine Equivalent Dose in the Opioid Crisis

To address this crisis, both countries have sought to implement strategies to control and monitor opioid use more effectively. One such strategy is the use of the Morphine Equivalent Dose (MED), a tool designed to standardize the measurement of opioid potency [3].

Overall, the implementation of MED monitoring in both countries signifies a crucial step towards mitigating the opioid crisis, with a particular emphasis on the U.S. due to its unique challenges and the scale of the epidemic.

In the U.S., information about all drugs, including opioids, is maintained in the Food and Drug Administration's (FDA) National Drug Code (NDC) database [4,5]. The Drug Product Database (DPD) in Canada is a detailed repository of all drugs sold in the country, including opioids, and is updated nightly [4–6].

This R package, designed to leverage both U.S. and Canadian opioid prescription data, aims to help researchers fill a significant gap in the current landscape of opioid management tools [4]. The package is informed by guidelines such as the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain [7] and the 2022 Clinical Practice Guideline for Prescribing Opioids for Pain, issued by the Centers for Disease Control and Prevention (CDC) [8]. Additionally, it incorporates methodologies from various U.S.-based MED calculators, like the Morphine Milligram Equivalents (MME) Calculator by MDCalc [1] and the Oregon Pain Guidance calculator [1], which are both aligned with the 2022 Clinical Practice Guideline for Prescribing Opioids for Pain, issued by the Centers for Disease Control and Prevention [8–10]. The Ohio Automated Rx Reporting System's conversion factors, created by the CDC, are also considered [11]. The MME values calculated by this package show a perfect correlation to those from the above-mentioned opioid calculators [1].

What sets this R package apart is its capability to process the DIN for Canadian drugs or National Drug Code for U.S. drugs, and output the MED, a feature not commonly found in existing open-source software. This functionality is particularly crucial for research purposes, allowing for a more in-depth analysis of opioid prescription trends and long-term patterns. Such insights are essential for developing better clinical guidelines and improving patient outcomes.

The OralOpioids R package is tailored for researchers interested in the comprehensive study of opioid prescriptions in Canada and the U.S. By automating the MED calculation process it enables a more nuanced understanding of opioid use patterns and their implications.

The novelty of our study lies in the development and extension of the OralOpioids R package, a pioneering tool that integrates opioid prescription data from both Canada and the United States. This package uniquely automates the retrieval, processing, and analysis of opioid-related data from Health Canada's Drug Product Database and the FDA's National Drug Code database, incorporating the Morphine Equivalent Dose (MED) calculation—a feature not commonly found in existing open-source software. By bridging data from two countries with significant opioid challenges, the study provides a comprehensive platform for researchers to compare and contrast opioid prescribing patterns, enabling deeper insights into the opioid crisis on a North American scale. This innovative approach not only enhances research capabilities but also offers potential applications in public health, policy-making, and clinical practice, aiming to inform and improve strategies for opioid management and harm reduction.

2. Materials and Methods

SQUIRE 2.0 guidelines were followed when designing this study [12]. This study utilizes an R package developed to automate the collection and analysis of opioid data

from Health Canada and the U.S. FDA. The package OralOpioids was first available on CRAN in February 2023. Initially, the package only focused on Canadian opioids. The details of the Canadian subset of the package are available here [1]. The authors of the package decided to include FDA data on Oral Opioids given the opioid epidemic in the US. The package's core function, load_Opioid_Table, selectively retrieves opioid-related data based on the specified country (Canada or the U.S.). This function is a critical component of our methodology, enabling streamlined data acquisition and processing, which are vital for our comparative analysis. This is a new function compared to our previous study [1].

1. Data Retrieval Functionality:
    - The function load_Opioid_Table serves as an interface to two country-specific functions: load_HealthCanada_Opioid_Table and load_FDAOpioid_Table.
    - It accepts the country name as an argument and, based on this, calls the respective function to obtain the latest opioid data from the relevant national database.
2. Health Canada Data Processing (load_HealthCanada_Opioid_Table):
    - This function checks the local file's date against the latest data date from Health Canada [1]. If the local file is outdated, it downloads, updates, and processes the new data.
    - Data processing includes filtering, standardizing, and organizing various attributes like Drug Identification Number (DIN), dosage, form, and route of administration. It is an eight-digit number assigned by Health Canada to each drug product approved for sale in Canada.
3. FDA Data Processing (load_FDAOpioid_Table):
    - Similar to the Health Canada function, this function manages data from the FDA. It checks and updates the opioid data files based on the most recent information available from the FDA database.
    - The data are then processed to align with the analysis requirements, focusing on attributes like the National Drug Code (NDC), active ingredients, and pharmaceutical classification. NDC stands for National Drug Code, a unique identifier for medications in the United States. It is a 10- or 11-digit number assigned by the U.S. Food and Drug Administration (FDA) to identify each drug product approved for commercial distribution. The NDC is used for tracking and identifying drugs in the U.S. and is an essential component of the healthcare system, especially for pharmacies, healthcare providers, and insurance companies.
    - The user needs to enter the entire NDC with a hyphen in the format 4–4, 5–3, or 5–4, meaning that there are 4 or 5 digits for the labeler code and 4 or 3 digits for the product code. They do not need to enter the second hyphen and the numbers after that.
4. MED Calculations and Data Integration:
    - Both functions incorporate mechanisms to calculate the MED for various opioid products, a crucial step in analyzing opioid potency and usage patterns.
    - The final output is a comprehensive dataset that combines relevant opioid data, tailored to the requirements of our study, focusing on dosage, formulation, and regulatory status.

The OralOpioids R package processes opioid data for both the U.S. and Canada through a systematic approach. See here for details on the Canadian content [1]:

1. U.S. Opioid Data Processing (See Figure 1a):
    - Initiation: Begin the data processing procedure.
    - Country Choice: Select the U.S. for data extraction.
    - Data Acquisition: Retrieve the latest FDA opioid data, updating local data if necessary.
    - Data Filtration: Filter the dataset for routes like Oral, Transdermal, Rectal, Buccal, and Sublingual, as classified by the FDA.

- Removal of Non-Opioid Elements: Isolate and remove non-opioid elements, focusing on opioid-based ingredients.
- Additional Filtering: Apply further filters to meet specific U.S. regulatory requirements and drug characteristics.
- MED Calculation: Calculate the Morphine Equivalent Dose (MED) for the opioids.
- Dataset Finalization: Complete dataset preparation for analytical use.
- Output: Provide the processed U.S. opioid data for further analysis.
- Completion: Conclude the U.S. data processing.

2. Canadian Opioid Data Processing (Figure 1b):

Figure 1a: Flowchart for US opioids

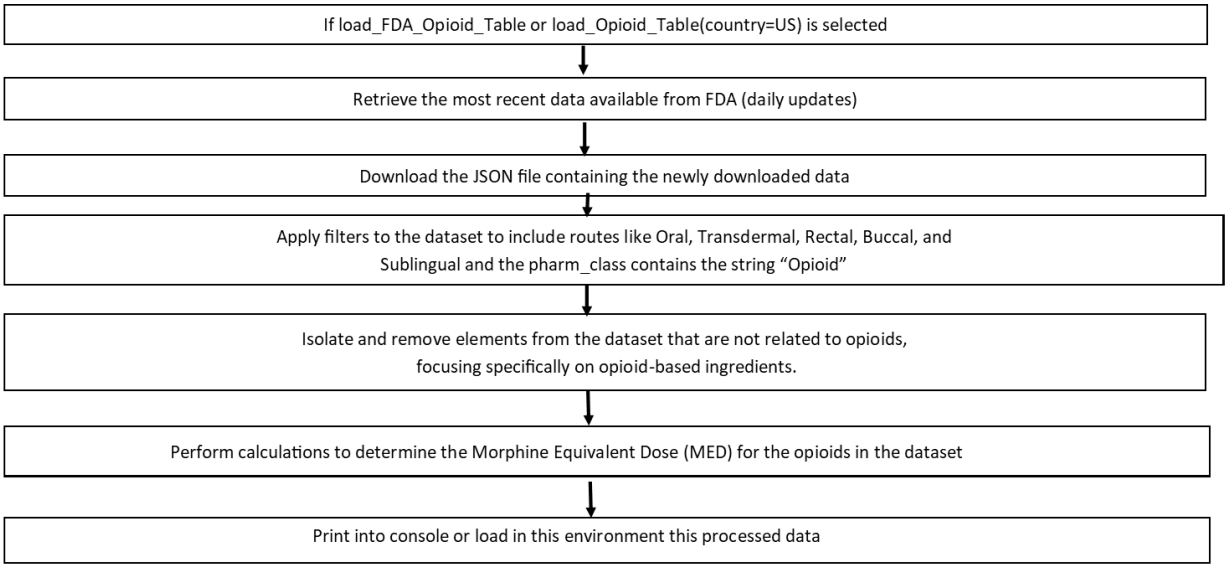

Figure 1b: Flowchart showing processing of Canadian opioids

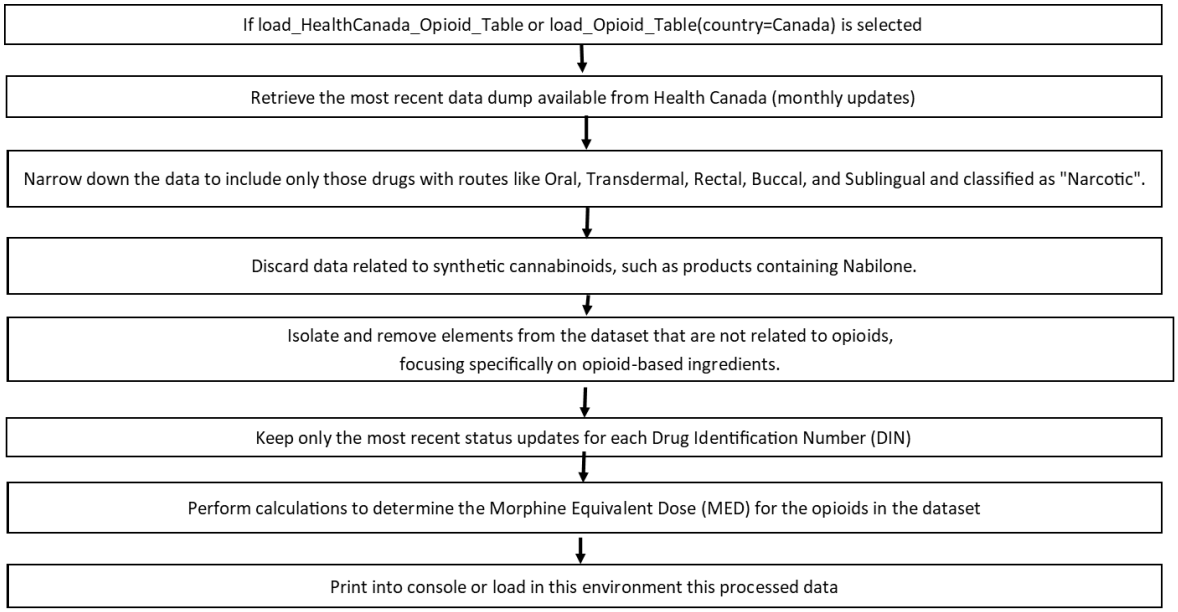

Figure 1. (**a**) Flowchart showing the working of load_Opioid_Table (country = “us”) or load_FDA_Opioid_Table. (**b**) Flowchart showing the working of load_Opioid_Table (country = “ca”) or load_HealthCanada_Opioid_Table.

Both processing paths in the OralOpioids package are designed to systematically retrieve, filter, and analyze opioid data, tailored to the regulatory environments and specific data structures of the U.S. and Canada. The process ensures the datasets are comprehensive and ready for in-depth analysis and research applications. Further details are available here [1].

3. Results

There are three important functions, namely load_HealthCanada_Opioid_Table, load_FDA_Opioid_Table, and load_Opioid_Table, enabling the R programmer to download the most recent data for opioid prescriptions authorized by Canada and the U.S., respectively. The function load_Opioid_Table gives the user the option to select either U.S. or Canada and selects either load_HealthCanada_Opioid_Table (Canada) or load_FDA_Opioid_Table (US) depending on the country selected. In August 2024, for U.S. opioids, there were 1741 oral opioids authorized for sale by the FDA as identified by the function load_FDA_Opioid_Table or if the U.S. was selected in load_Opioid_Table. See Figure 2 for a table summarizing the distribution of opioid medications authorized for sale in the U.S. and Canada as of August 2024, classified by Morphine Equivalent Dose (MED) per dispensing unit (per tablet for oral solids and per ml for oral liquids) and Table 1 for count of unique opioid medications in U.S. and Canada based on opioid type.

MED per dispensing unit	Count of Canadian opioids	Count of US opioids
Less or Equal to 1.5	115	91
Between 1.5 to 5	82	307
Between 5 to 20	100	501
Between 20 to 50	75	208
Above 50	121	133

Figure 2. Summarizes the number of oral opioids whose MED is calculated in the package.

Table 1. The no. of DIN and NDCs in the package.

Opioid	US	Canada
Anileridine	*NA* [1]	1
Buprenorphine	126	35
Codeine	156	214
Dextropropoxyphene	*NA* [1]	7
Dihydrocodeine	1	*NA* [1]
Fentanyl	49	86
Hydrocodone	286	30
Hydromorphone	53	63
Levorphanol	9	*NA* [1]
Loperamide	227	*NA* [1]
Meperidine	6	1
Methadone	56	26
Methylnaltrexone	1	*NA* [1]
Morphine	143	121
Naloxone	58	24
Naltrexone	27	*NA* [1]

Table 1. *Cont.*

Opioid	US	Canada	
Normethadone	*NA* [1]		6
Opium	NA [1]		11
Oxycodone	313		94
Oxymorphone	28		5
Pentazocine	6		1
Samidorphan	16	*NA* [1]	
Sufentanil	1	*NA* [1]	
Tapentadol	8		16
Tramadol	192		48

[1] NA denotes that particular opioid type was not authorized to be sold as an oral opioid in that particular country.

The dataset can either be printed in the console and automatically downloaded as a spreadsheet in the package library [4].

Every time a function is run, the spreadsheet will verify if it contains the most recent data from either Health Canada or the FDA, depending on whether Canada or the U.S. has been selected. If the spreadsheet is out of date and the user confirms by selecting "Y", the system will attempt to download the required data. Once the data are successfully downloaded and updated, the system will generate a confirmation message indicating that the Opioid_Table has been updated to the most recent date.

The package includes functions that pull specific details about prescription drugs from a dataset based on their DIN or NDC, as shown in Table 2. See the Supplementary Materials for the vignette that illustrate examples.

Table 2. Description of functions in the R package.

Function	Description
load_Opioid_Table	The function load_Opioid_Table serves as an interface to two country-specific functions: load_HealthCanada_Opioid_Table and load_FDA_Opioid_Table. It accepts the country name as an argument and, based on this, calls the respective function to obtain the latest opioid data from the relevant national database. The final output is a comprehensive dataset that combines relevant opioid data, focusing on dosage, formulation, and regulatory status.
load_FDA_Opioid_Table	This function checks and updates the opioid data files based on the most recent information available from the FDA database. This information is uploaded daily. The data are then processed to align with the analysis requirements, focusing on attributes like the National Drug Code, active ingredients, and pharmaceutical classification.
load_HealthCanada_Opioid_table	This function checks the local file's date against the latest data date from Health Canada. If the local file is outdated, it downloads, updates, and processes the new data. Data processing includes filtering, standardizing, and organizing various attributes like DIN, dosage, form, and route of administration.
MED	This function calculates the Morphine Equivalent Dose for a particular drug using its DIN or NDC for Canadian or American Opioids, respectively. The MED standardizes opioid potency across different medications, allowing for meaningful comparisons and informed prescribing decisions
MED_50	This function computes the no. of units (tables or ml for liquids) corresponding to the 50 MED thresholds, respectively, as outlined in the 2022 CDC guidelines [8]. These threshold values aid healthcare providers in making well-informed decisions about dosage adjustments and addressing potential safety concerns.

Table 2. *Cont.*

Function	Description
MED_90	This function computes the no. of units (tables or ml for liquids) corresponding to the 90 MED thresholds.
Opioid	Determines the opioid content of a drug using its DIN/NDC, essential for assessing medication potency and adjusting dosages properly.
Brand	Retrieves the brand name for a specific oral opioid using its DIN/NDC, facilitating clearer communication between healthcare providers and patients regarding medication prescriptions.

4. Discussion

The opioid crisis in the United States has reached alarming levels, with a significant increase in opioid-related fatalities and addiction rates over the past decade. This crisis underscores the urgent need for strategic interventions that regulate opioid consumption effectively. One such strategy is the use of Morphine Equivalent Dose (MED), which standardizes the potency of different opioids relative to morphine. While MED is a crucial tool in managing opioid dosages, its calculation is complex, requiring detailed knowledge of each opioid's content and dosage form. This study expands the capabilities of the OralOpioids R package by integrating opioid-related data from both Canada and the United States, offering a comprehensive platform for cross-national analysis of opioid prescribing practices.

Our approach differs from existing studies by focusing on the integration of opioid data from two major countries facing significant opioid-related challenges. Previous research has primarily focused on either the U.S. or Canada, analyzing opioid prescription patterns, overdose rates, and the effectiveness of regulatory interventions. For instance, the study by Bohnert et al. (2018) [13] in the United States highlighted the role of MED thresholds in opioid prescribing guidelines and their potential impact on reducing opioid-related harm. Similarly, Gomes et al. (2014) explored the relationship between high-dose opioid prescribing and opioid-related mortality in Canada [14]. However, these studies did not provide any tools to calculate MED in a user-friendly fashion.

The OralOpioids package addresses this gap by providing a tool that not only retrieves and processes opioid data from both the FDA and Health Canada but also automates the calculation of MED for various opioid products. This integration allows for a more nuanced analysis of opioid formulations and regulatory differences between the two countries. Unlike other studies that rely on manual data processing or focus on specific opioid classes or regions, our package offers a standardized and automated approach, reducing the potential for human error and ensuring consistent data analysis across different datasets.

The influence of opioid stewardship initiatives and evolving regulatory landscapes on prescribing trends also cannot be overlooked. Recent guidelines, including the revised 2022 CDC opioid prescribing guidelines, emphasize a more individualized approach to opioid therapy [8]. These guidelines recommend shared decision-making and highlight the importance of considering patient-specific factors when managing opioid use. This shift away from rigid adherence to MED thresholds aims to prevent potential harms associated with abrupt discontinuation or rapid tapering of opioid use. Our findings align with these guidelines, reinforcing the idea that while MED is a valuable tool for standardizing opioid potency, it should not dictate clinical decisions in isolation.

In contrast to other studies, which often provide a retrospective analysis of opioid prescribing trends, the OralOpioids package is designed as a proactive tool for researchers and healthcare professionals. By offering real-time data processing and MED calculations, it facilitates the ongoing monitoring of opioid prescribing practices, enabling timely interventions and policy adjustments. The inclusion of both active and discontinued opioids in the dataset allows for a comprehensive analysis of historical and current prescribing practices, providing insights into the evolution of opioid use over time.

The package's user-friendly nature and the easy availability of information on Canadian and U.S. opioids make it accessible to a wide range of users. This accessibility fosters collaborative research and the development of unified strategies to address the opioid crisis across North America. By offering a platform for cross-national research, the OralOpioids package not only contributes to the existing body of knowledge but also paves the way for future studies that can explore the global impact of opioid prescribing practices.

4.1. Comparison with Other Studies

In comparison to studies like those of Bohnert et al. (2018) [13] and Gomes et al. (2014) [14], which provided critical insights into opioid prescribing practices within single countries, our study introduces a novel cross-national perspective to calculate MED to the researchers with access to prescription patterns. While these studies contributed significantly to understanding opioid misuse within their respective contexts, they did not address the broader North American framework that our study seeks to explore. Additionally, unlike studies that utilize retrospective data analysis, our research emphasizes the proactive application of real-time data processing through the OralOpioids package, offering a dynamic tool for ongoing research and public health interventions.

4.2. Novelty and Impact

What sets our study apart is the development and application of the OralOpioids R package as a cross-national tool for analyzing opioid prescribing practices in both Canada and the U.S. This package automates the retrieval and processing of opioid data from national databases, offering standardized MED calculations that are crucial for safe prescribing practices. By enabling a comprehensive and comparative analysis of opioid use across two major countries, our study provides valuable insights that can inform public health strategies and clinical guidelines. The OralOpioids package represents a significant advancement in the field of opioid research, with the potential to influence policy and improve patient outcomes on a broader scale.

4.3. Limitations

While our study provides a valuable tool for researchers, it is essential to remain aware of its limitations. The data does not capture real-time prescribing data nor does it reflect the actual consumption of dispensed medications. Future research aims to integrate actual prescribing data, perhaps via collaborations with healthcare databases and national prescription claims, to provide a more accurate picture of opioid use patterns. The databases used do not provide information regarding the medical diagnoses associated with opioid prescriptions. This gap prevents a deeper understanding of the appropriateness of opioid use, such as whether opioids are being prescribed for conditions where they are indicated. By focusing on authorized drugs rather than those actually dispensed and consumed, our study does not account for medication waste—opioids that are prescribed and dispensed but ultimately not used by patients. This aspect could lead to overestimations of actual opioid exposure in the population and obscure issues related to medication accumulation and disposal.

5. Practical Applications and Future Directions

The OralOpioids package demonstrates diverse applications, from aiding healthcare providers in effective pain management to assisting insurance companies and workers' compensation boards in monitoring opioid use by integrating the concept of Morphine Equivalent Dose (MED) within prescription databases. Its practical value is highlighted in its ability to identify high-risk opioid dosages and influence medical aid policies. Moreover, the authors suggest that adapting this tool for use in other countries could significantly enhance its global relevance, making it a versatile resource for addressing the opioid crisis on an international scale.

Instructions on usage: The primary users of this package are expected to be public health researchers with access to prescription patterns via NDCs and DINs for the U.S. and Canada, respectively. For instance, if a researcher has access to prescription patterns that have the NDC or DIN in them, they would need to extract all the opioid prescriptions within a specified period (say within 30 days). These prescription databases would also detail the doses dispensed. Using the OralOpioids package, the total MED dispensed for that individual in a period could be calculated. Daily MED could be calculated by dividing the total MED for that individual by the number of days of the study period. A value greater than 90 MED/day indicates a very high risk for opioid-related complications. This tool would enable them to identify individuals at high risk for opioid abuse more effectively. However, it is important to clarify that the OralOpioids package is not intended to replace clinical judgment but rather to augment it by providing accurate and efficient MED calculations. This automation ensures a reduction in manual errors, saving time and promoting safer opioid prescribing practices.

6. Conclusions

In summary, the OralOpioids R package, with its comprehensive opioid data analysis capabilities and precise MED calculations, is poised to play a crucial role in the United States' efforts to combat the opioid epidemic. Its potential to streamline opioid monitoring and promote safer prescribing practices positions it as an invaluable tool not only for researchers and public health professionals but also for broader applications in pain management and healthcare policy. This package's adaptability and utility underscore its importance in the ongoing battle against opioid misuse and its consequences.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/biomedinformatics4030112/s1. Supplementary Materials: OralOpioid.pdf.

Author Contributions: A.B.: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing—original draft, Writing—review and editing. E.S.: Methodology, Software, Validation, Writing—review and editing, Senior Technical author. D.T.N.: Writing—review and editing. K.N.: Review. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: No ethics approval was needed as all the data used for this study are available publicly and are de-identified.

Informed Consent Statement: No consent is needed as the data are publicly available.

Data Availability Statement: The Food and Drug Administration (FDA) Database metadata is available for download from https://download.open.fda.gov/drug/ndc/drug-ndc-0001-of-0001.json.zip (accessed on 31 August 2024). The Health Canada Drug Product Database metadata (Data Dump) is available for download from https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database/what-data-extract-drug-product-database.html (accessed on 31 August 2024). The OralOpioids package is available for download from CRAN. https://cran.r-project.org/web/packages/OralOpioids/index.html (accessed on 31 August 2024). The Shiny app where a user can input a Drug ID for details is available at http://ankonacanada.shinyapps.io/Opioidpaper. Some examples are also available.

Acknowledgments: Erik Stricker and Ankona Banerjee contributed equally to the development of the R package.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Banerjee, A.; Stricker, E. OralOpioids: Harnessing R Programming and Data Science to Combat Opioid Misuse. *Health Serv. Res. Manag. Epidemiol.* **2023**, *10*, 23333928231208251. [CrossRef] [PubMed]

2. Centers for Disease Control and Prevention. Opioid Data Analysis and Resources. Available online: https://www.cdc.gov/overdose-prevention/data-research/facts-stats/index.html (accessed on 9 January 2024).
3. Lossio-Ventura, J.A.; Song, W.; Sainlaire, M.; Dykes, P.C.; Hernandez-Boussard, T. Opioid2MME: Standardizing opioid prescriptions to morphine milligram equivalents from electronic health records. *Int. J. Med. Inform.* **2022**, *162*, 104739. [CrossRef] [PubMed]
4. Banerjee, A.; Stricker, E. OralOpioids: Retrieving Oral Opioid Information. Available online: https://cran.r-project.org/web/packages/OralOpioids/index.html (accessed on 31 August 2024).
5. US Food and Drug Administration. National Drug Code Directory. Available online: https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory (accessed on 31 August 2024).
6. Government of Canada. Drug Identification Number (DIN). Available online: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drug-identification-number.html (accessed on 31 August 2024).
7. Busse, J.W.; Craigie, S.; Juurlink, D.N.; Buckley, D.N.; Wang, L.; Couban, R.J.; Agoritsas, T.; Akl, E.A.; Carrasco-Labra, A.; Cooper, L.; et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ* **2017**, *189*, E659–E666. [CrossRef] [PubMed]
8. Dowell, D.; Ragan, K.R.; Jones, C.M.; Baldwin, G.T.; Chou, R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain—United States, 2022. *MMWR Recomm. Rep.* **2022**, *71*, 1–95. [CrossRef] [PubMed]
9. Motov, S. Morphine Milligram Equivalents (MME) Calculator. Available online: https://www.mdcalc.com/calc/10170/morphine-milligram-equivalents-mme-calculator (accessed on 31 August 2024).
10. Oregon Health Authority. Opioid Conversion Calculator. Available online: https://www.oregonpainguidance.org/opioidmedcalculator/ (accessed on 31 August 2024).
11. State of Ohio Board of Pharmacy. Ohio Automated Rx Reporting System OARRS. Available online: https://www.ohiopmp.gov/MED_Calculator (accessed on 31 August 2024).
12. Ogrinc, G.; Davies, L.; Goodman, D.; Batalden, P.; Davidoff, F.; Stevens, D. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): Revised publication guidelines from a detailed consensus process. *BMJ Qual. Saf.* **2016**, *25*, 986–992. [CrossRef] [PubMed]
13. Bohnert, A.S.B.; Guy, G.P., Jr.; Losby, J.L. Opioid Prescribing in the United States Before and After the Centers for Disease Control and Prevention's 2016 Opioid Guideline. *Ann. Intern. Med.* **2018**, *169*, 367–375. [CrossRef] [PubMed]
14. Gomes, T.; Mamdani, M.M.; Dhalla, I.A.; Cornish, S.; Paterson, J.M.; Juurlink, D.N. The burden of premature opioid-related mortality. *Addiction* **2014**, *109*, 1482–1488. [CrossRef] [PubMed]