International Journal of Population Data Science

Journal Website: www.ijpds.org

Medication Use Trajectories in Chronic Pain: Comparing Risk-Based and Count-Based Approaches Using Linked Prescription Claims Data

Hermine Lore Nguena Nguefack[1], Nancy Ménard[2], Sylvie Beaudoin[2], M. Gabrielle Pagé[3,4], Line Guénette[5,6], Catherine Hudon[7], and Anaïs Lacasse[1,*]

Submission History

Submitted:	09/09/2025
Accepted:	09/08/2026
Published:	04//11/2026

[1] Department of Health Sciences, Université du Québec en Abitibi-Témiscamingue (UQAT), 445 boulevard de l'Université, Rouyn-Noranda (QC), J9X 5E4, Canada
[2] Patient partner, Rouyn-Noranda (QC), Canada
[3] Research Center, Centre hospitalier de l'Université de Montréal (CHUM), 900 rue Saint-Denis, Montréal (QC), H2X 0A9, Canada
[4] Department of Anesthesiology and Pain Medicine, Faculty of Medicine, Université de Montréal, 2900, boulevard Édouard-Montpetit, Montréal (QC), H3T 1J4, Canada
[5] Population Health and Optimal Health Practices Research Unit, CHU de Québec Research Center – Université Laval, 1050 chemin Sainte-Foy, J1-08, Québec (QC), G1S 4L8, Canada
[6] Faculté de pharmacie, Université Laval, 1050 avenue de la Médecine, local 2345, Québec (QC), G1V 0A6, Canada
[7] Family Medicine and Emergency Medicine Department, Université de Sherbrooke, 3001 12e avenue Nord, Sherbrooke (QC), J1H 5N4, Canada

Abstract

Introduction
In the context of chronic pain, no study has yet compared risk-based and count-based approaches for modelling medication use trajectories. Risk-based approach reflects the potential burden of medication-related adverse effects, whereas count-based approach reflects treatment burden and regimen complexity. Comparing these complementary measures may identify different patient profiles depending on the clinical or research objective.

Objectives
This study aimed to compare a composite medication risk score, the Medication Quantification Scale 4.0 (MQS-4.0), with medication count in examining medication use trajectories among individuals with chronic pain.

Methods
We conducted a cohort study using data from the TorSaDE Cohort, which links five cycles of Statistics Canada's Canadian Community Health Survey (2007-2016 cross-sectional questionnaires) and Québec provincial health administrative databases (1996-2016 longitudinal data). We selected 8,760 adults with chronic pain who were covered by public prescription drug insurance. Pain-related medications used in the two-year period following survey completion were operationalised as monthly risk scores and monthly medication count. Growth Mixture Modelling was applied to each of these measures to identify groups with similar patterns over time (trajectories).

Results
Both the MQS-4.0 risk score and the medication count were effective in forming trajectory groups that were statistically robust (based on entropy and Bayesian information criterion) and clinically meaningful. However, the MQS-4.0 risk score approach was more discriminative, identifying differences between trajectory groups in terms of sociodemographic characteristics, pain profiles, health status, and healthcare utilisation. Individuals with the highest pain-related medication count did not necessarily have the highest MQS-4.0 risk scores, and some individuals using fewer medications were found to be at high risk.

Conclusions
Our findings suggest that a risk-based approach such as the MQS-4.0 may provide complementary information to a count-based approach for subgroup analyses, particularly when using health administrative databases to study pain-related medication use in individuals living with chronic pain.

Keywords
chronic pain, polypharmacy, analgesics, medications, risk, trajectories, medication quantification scale, growth mixture modelling, health administrative data

Highlights

- This study compares a risk-based (MQS-4.0) approach to a count-based approach for modelling medication use trajectories in chronic pain.
- Both approaches identified statistically robust trajectory groups, but MQS-4.0 was more discriminative in differentiating sociodemographic, pain, and health characteristics.
- The study highlights that high medication count does not always correlate with high risk, thus challenging traditional assumptions.
- Results suggest that risk-based approach such as the MQS-4.0 may provide complementary information to a count-based approach for subgroup analyses.

*Corresponding Author:
Email Address: lacassea@uqat.ca (Anaïs Lacasse)

https://doi.org/10.23889/ijpds.v11i1.3350
November 3, 2026 © The Authors. Open Access under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/deed.en)

Introduction

Chronic pain (CP) affects one in five adults [1, 2] and is clinically defined as pain that persists or recurs over more than three months [3]. In 2019, the annual financial burden of CP in Canada in terms of healthcare and lost productivity was estimated at $38.3–40.4 billion [4]. CP treatment involves a combination of physical and psychological therapy (physiotherapy, meditation, psychotherapy, etc.), in addition to medication [4]. Polypharmacy, defined as the concurrent use of multiple medications [5], is highly prevalent in this population [6, 7]. A recent Canadian study highlights that 71% of adults living with CP concomitantly use five or more medications (a common threshold for polypharmacy), while 26% concomitantly use 10 or more medications (i.e., excessive polypharmacy) [8]. Although polypharmacy can lead to positive outcomes by approaching pain through multiple mechanisms of action, many medications can pose substantial risks, including adverse effects [9, 10], drug interactions [9, 10], drug cascades [11], as well as depression [12], lower quality of life [13], and mortality [14, 15].

Seeing that individuals living with CP have varying medication regimens that involve different therapeutic classes and dosages that change over time [16, 17], it is essential to gain a better understanding of the risk associated with medication use among individuals living with CP over time (risk trajectories). Trajectory analyses rely on person-centred statistical approaches to identify subgroups of individuals with similar longitudinal patterns [18]. Identifying these distinct trajectories helps characterise individuals at greater or lower risk of adverse outcomes and provides insight into the modifiable factors associated with each trajectory. Such knowledge can guide the development of tailored interventions aimed at improving outcomes among high risk groups. In CP pharmacological treatment, a research tool designed to quantify the risk associated with pain-related medications, the Medication Quantification Scale (MQS), was developed in 1992 and various versions were validated [19–25]. Its fourth version (the MQS-4.0) has been validated in Canadian practice [22].

The relevancy of composite medication risk scores, such as the MQS-4.0, is expected as the associated risk of adverse effects is not always directly proportional to the number of medications taken. However, such scores sometimes require complex calculations. It is therefore worth questioning whether simply counting the number of medications offers comparable value for research purposes.

This study thus aimed to compare a composite medication risk score, the Medication Quantification Scale 4.0 (MQS-4.0), with a count-based approach in examining medication use trajectories among individuals with CP. Our intention was to examine how a risk-based measure and a count-based measure may differently classify medication use trajectories in a real-world chronic pain population. Although related, medication risk and medication count represent distinct constructs. Medication count primarily reflects treatment burden and regimen complexity, whereas the MQS-4.0 incorporates information on medication classes to better estimate the potential burden of medication-related adverse effects. Consequently, the choice of measure should depend on the research or clinical objective. A count-based approach may be appropriate when examining polypharmacy prevalence, healthcare resource use, or medication regimen complexity, while a risk-based approach may be more informative when studying medication safety, adverse effects, deprescribing priorities, or identifying individuals who may benefit from medication review. Specifically, we compared these two approaches based on: (1) their utility in creating trajectory groups (i.e., individuals with similar patterns over time) that are statistically robust and clinically interpretable; (2) their ability to generate trajectory groups that are distinct in terms of sociodemographic profiles, pain characteristics, health status, and healthcare utilisation; and (3) the overlap between the high risk or high-count individuals identified respectively through the MQS-4.0 risk score trajectory analysis and the count-based trajectory analysis. We hypothesised that heavy users of pain medication are not necessarily at higher risk of adverse effects per the MQS-4.0 score, and individuals using fewer medications may still face substantial risk.

Methods

This manuscript is reported in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement.

Design

This retrospective cohort study used data from the TorSaDE Cohort (n = 102,148) [26], a research infrastructure linking five cycles of Statistics Canada's Canadian Community Health Survey (2007-2008 to 2015-2016 cross-sectional questionnaires) and Québec provincial health administrative databases (1996-2016 longitudinal data).

Data Sources

The TorSaDE Cohort has been described in detail elsewhere [26].

Canadian Community Health Survey

This Statistics Canada survey collects health and socioeconomic data on Canadians aged 12 and older using probability sampling [27]. Standardised questionnaires are used and data quality is maximised through a variety of methods, including rigorous interviewer training and various control measures.

Health Administrative Databases

In Canada's universal healthcare system, public health insurance covers medical consultations, emergency visits, hospitalisations, and procedures for all Québec residents, except those with temporary permits [28]. Prescription drug coverage is mandatory through public or private plans. The public prescription drug insurance plan covers individuals who: 1) lack private drug insurance; 2) are aged 65 or older; or 3) receive last-resort financial assistance. These groups represent approximately 46% of the Québec population [28], and 57 to 68% of individuals living with CP [29, 30]. The pharmaceutical services database contains detailed information on prescription

drugs dispensed in the community and covered by the public prescription drug plan [31].

Linkage and Data Access

When taking part in the Canadian Community Health Survey, participants give informed consent to Statistics Canada for the linkage of their responses to provincial health administrative databases and use for research purposes. Any given survey year, 90% to 95% of survey participants consent to the linkage with data from other sources for research purposes. Linkage with administrative data was possible for more than 95% of participants (person-level linkage) [26]. The linkage was conducted by the *Institut de la statistique du Québec*, the official government agency responsible for collecting, producing, and disseminating statistical information about Québec. De-identified data from the TorSaDE Cohort was accessed via the secure server of the *Institut de la statistique du Québec* (ISQ), which acts as the mandated data access authority. The preparation and cleaning of the TorSaDE Cohort data then required over 1,000 hours of work by our team's experienced biostatisticians specialised in the analysis of large-scale administrative databases, ensuring high data quality and reliability for research purposes. Ethical approval was obtained from the Commission d'accès à l'information du Québec (#1013990), the Institut de la statistique du Québec (ISQ), and relevant university Research Ethics Boards (Université du Québec en Abitibi-Témiscamingue: #2018-02-Lacasse, A.; Centre hospitalier universitaire de Sherbrooke (CHUS): #2017-1504).

Study Population and Selection Criteria

This study included 8,760 individuals selected according to the following criteria applied to the TorSaDE Cohort: **(1)** for individuals with more than one survey participation, only the first participation was retained; **(2)** individuals reporting CP : individuals who answered "No" to the survey question "*Are you usually free of pain or discomfort?*"—while this definition may differ from commonly used definitions of chronicity based on the duration of symptoms [3, 32], it has been used in many CP epidemiology studies [33–48] and provides prevalence estimates (17-22% [33, 35, 36, 46]) comparable to those obtained in studies using a more traditional definition (20-21% [1, 2]) during similar periods; **(3)** individuals aged 18 years or older; and **(4)** individuals covered by the public prescription drug insurance plan during the two years following their participation in the Canadian Community Health Survey.

Study Variables

Analgesic and co-prescribed medication use (hereafter referred to as pain-related medications) was operationalised using two approaches for comparison: the MQS-4.0 risk score and the number of medications used.

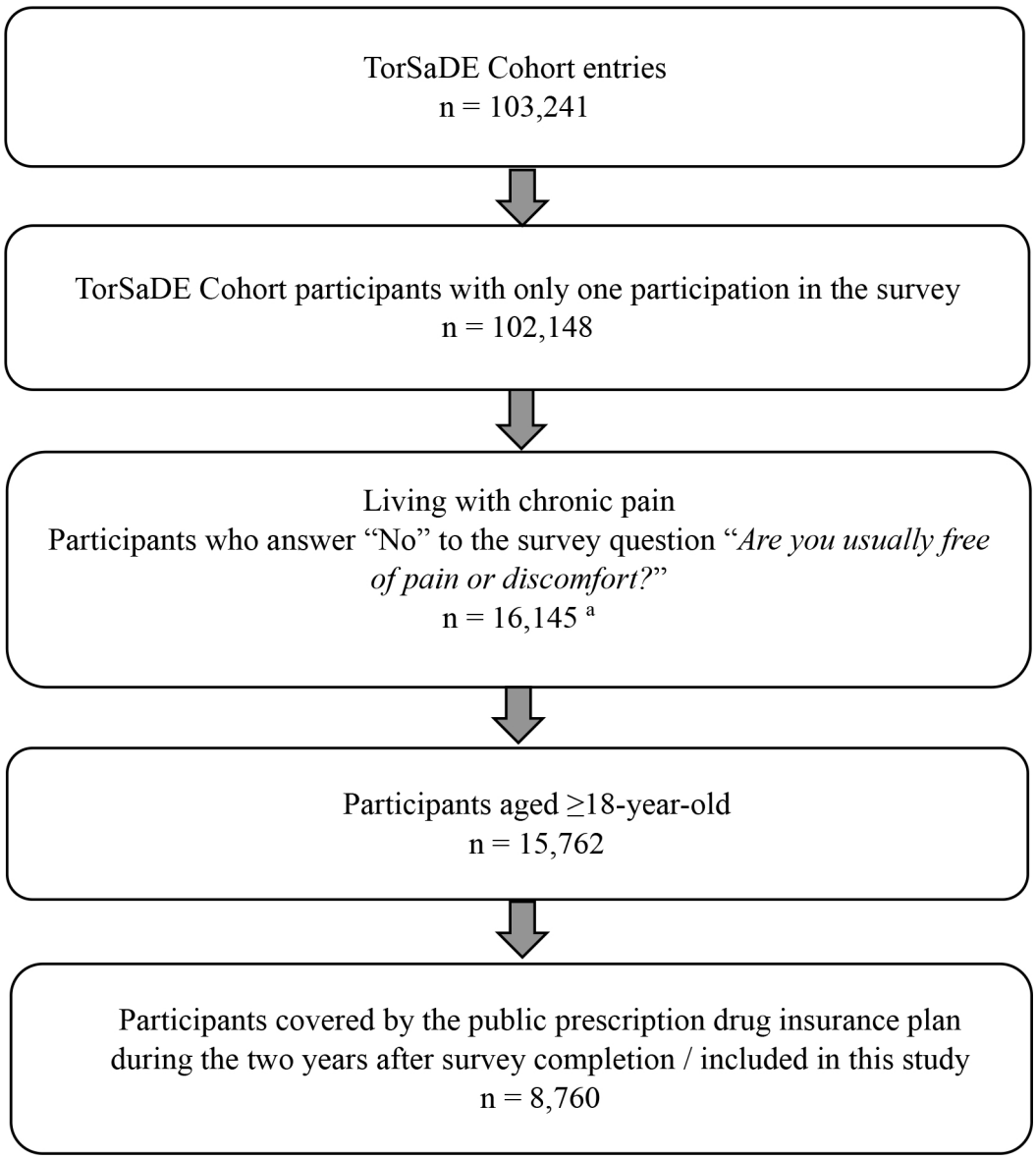
MQS-4.0 Risk Score

The MQS-4.0 is a validated research tool designed to quantify the risk associated with 36 medication subclasses used for CP management and associated comorbidities (e.g., sleep, mood) (Supplementary Appendix 1) [22]. The MQS-4.0 reflects the overall risk of short- or long-term adverse effects caused by medications [22]. Pain-related medications were assigned weights (points), which could then be summed to compute a composite risk score, where higher scores mean higher risk of adverse effects. Just like previous versions of the tool, the MQS-4.0 weighting system is grounded in the clinical judgement of prescribers. Specifically, weights were derived from the median scores on a 0–10 scale assigned to each medication subclass in a Canadian survey in which physicians, pharmacists, and nurse practitioners who prescribed or adjusted analgesic medications in their clinical practice evaluated the level of risk associated with different medications. The definition of the overall risk of medication was specified to participants before survey completion, that is, "overall risk of medication to cause a short- or long-term adverse reaction, such as organ-specific or systemic toxicity (gastrointestinal symptoms, central nervous system), medication interactions, physical or psychological dependence potential, abuse potential, insomnia, tolerance, increased pain perception over time (hyperalgesia), and memory or concentration problems". Approximately 11% of respondents were chronic pain experts, while the remaining participants practised in primary care or other clinical specialties [22]. Consequently, the weights used to calculate MQS-4.0 scores reflect perspectives drawn from diverse real-world clinical practice settings. The Medication Quantification Scale (MQS), was developed in 1992 [21]. Updated in 1998 (MQS-II) [20], in 2003 (MQS-III) [19], and in 2022 by our team (MQS-4.0) [22], it has been shown to be reliable, valid, and sensitive to change [19–25]. The MQS was used as the quantification of the risk associated with pain medications use in a large number of pain studies between 2000 and 2026 [49–71], for instance as an outcome measure in various clinical trials on the impacts of interventions, or as a dependent, independent or control variable in observational studies. Our research team developed a valid SAS® algorithm to apply MQS-4.0 risk weights to prescribed drug insurance data [22], utilising American Hospital Formulary Service (AHFS) codes, supplemented at times by non-proprietary name codes (Supplementary Appendix 1). In our study, we used prescribed drug insurance data to calculate monthly MQS-4.0 risk scores (30-day periods) for each participant over the two years following the survey completion date.

Number of Medications (Medication Count)

Prescribed drug insurance data was used to calculate the monthly number of different pain-related medications used by each participant over the same two-year period. To enable an adequate comparison of the two approaches, only medications covered by the MQS-4.0 were included in this calculation, excluding those prescribed for other indications. For both approaches (MQS-4.0 risk score and medication count), participants were considered users of a specific medication in a given month if at least one claim for the medication was recorded during that month, regardless of prescription duration.

Figure 1: Study Sample Selection Flowchart



[a]No chronic pain n = 64,885; missing response to the question about pain n = 21,118; chronic pain percentage calculated using non-missing data = 16,145*100/(102,148-21,118)=19,9%.

Furthermore, we assessed medication use status at the time of survey completion using health administrative data. For this assessment, we applied a 90-day window to account for potential refill gaps [72]. Then, using the number of different pain-related medications used at least once in the 90-day period following survey completion, we classified participants based on medication count: five or more medications (i.e., polypharmacy), and 10 or more medications (i.e., excessive polypharmacy) [5, 73]. We followed the same approach for medications used across all therapeutic indications. As polypharmacy can also be defined as the use of two or more medications for a single health condition [74], we also applied this cut-off to classify participants based on the number of pain-related medications used.

Covariables

Variable selection aimed to describe our sample in terms of sociodemographic status, health status, and healthcare utilisation. Such self-reported variables included age, sex at birth, education level, relationship status, annual household income, administrative region of residence, pain intensity (none/mild/moderate/severe), activities prevented by pain or discomfort (none/a few/some/most), and self-perceived general health or mental health (fair/poor/good/very good/excellent). We used health administrative data to calculate the following variables during the two-year period following survey completion: continuity of care index (percentage of visits to the same practitioner [75]), number of different prescribers, and number of visits to a general practitioner, to a specialist, or to the emergency department. Administrative data covariables also included the number of hospitalisations (episodes), benzodiazepine use, and opioid use during the two-year period. We also considered all-cause mortality (dying at some point, after the end of the two-year period during which the trajectories were modelled) as descriptive outcome to characterise participants.

Table 1: Sample Characteristics

Characteristics[a] (n = 8,760)	**No. (%) of participants[b]**	
Sociodemographic profile		
Age (years) – mean ± SD	63.6	± 14.8
median (IQR)	66.0	(18.0)
Age (years) – n (%)		
18-24	143	(1.6)
25-44	817	(9.3)
45-64	3,042	(34.7)
≥ 65	4,758	(54.3)
Sex – n (%)		
Female	5,684	(64.9)
Male	3,076	(35.1)
Education level – n (%)		
No secondary diploma	3,600	(41.7)
Secondary diploma	1,112	(12.9)
College diploma/Registered apprenticeship or other trades certificate or diploma	2,934	(33.9)
University diploma	995	(11.5)
Relationship status – n (%)		
Not in a relationship	5,066	(57.7)
In a relationship	3,699	(42.3)
Annual household income (Can$) – n (%)		
< 20,000	2,964	(33.8)
20,000 -39,999	3,329	(38.0)
40,000 – 59,999	1,391	(15.9)
60,000 -79,999	592	(6.8)
≥ 80,000	484	(5.5)
Living in a remote region – n (%)		
No	6,384	(72.9)
Yes	2,376	(27.1)
Pain symptoms		
Pain intensity – n (%)		
Mild	1,759	(20.3)
Moderate	4,703	(54.2)
Severe	2,209	(25.5)
Activities prevented by pain or discomfort – n (%)		
None	3,001	(34.4)
A few	2,881	(33.1)
Some	1,456	(16.7)
Most	1,373	(15.8)
Health profile		
Self-perceived general health – n (%)		
Excellent, very good or good	5,254	(60.1)
Fair or bad	3,491	(39.9)
Self-perceived mental health – n (%)		
Excellent, very good or good	7,510	(89.1)
Fair or bad	923	(10.9)
All-cause mortality (died, at some point, after the 2-year period during which the trajectories were modelled) – n (%)		
No	8,214	(93.8)
Yes	546	(6.2)

Continued

Table 1: Continued

Characteristics[a] (n = 8,760)	No. (%) of participants[b]	
Healthcare and medication utilisation during the two years following survey completion		
Continuity of care index (%) – mean ± SD	84.7	± 20.6
median (IQR)	100.0	(28.6)
Number of different prescribers – mean ± SD	4.2	± 3.5
median (IQR)	3.0	(4.0)
Number of general practitioner visits – mean ± SD	6.8	± 6.3
median (IQR)	5.0	(6.0)
Number of specialist visits – mean ± SD	8.2	± 12.3
median (IQR)	5.0	(9.0)
Number of emergency department visits – mean ± SD	1.5	± 2.5
median (IQR)	1.0	(2.0)
Number of episodes of hospitalisation – mean ± SD	0.6	± 1.1
median (IQR)	0.0	(1.0)
Filled at least one prescription for benzodiazepines during the two years following survey completion – n (%)	2,940	(33.6)
Filled at least one prescription for opioids during the two years following survey completion – n (%)	2,011	(23.0)

[a]Proportion of missing data across presented variables ranged between 0.0% and 5.4%. Listwise deletion was applied for the subsequent analyses. [b]Unless stated otherwise. IQR: Interquartile range. SD: Standard deviation.

Statistical Analysis

We first described participant characteristics using descriptive statistics. We described baseline MQS-4.0 risk scores, the number of pain-related medications, and various polypharmacy classifications for the whole sample and across sex groups according to best practices [76].

Trajectory Groups

Growth Mixture Modelling (GMM) [18, 77] was applied to the monthly MQS-4.0 risk scores, and then to the monthly number of pain-related medications over the two-year period following survey completion. This analytical approach allowed for the grouping of individuals with similar outcomes (MQS-4.0 risk scores or medication count) over the two-year period following survey completion time. We then used trajectory group membership as a categorical dependent variable. We tested models with 1 to 6 trajectories using linear, quadratic and cubic shapes. We first tested the 18 models for the monthly MQS-4.0 risk scores, and then for the monthly number of pain-related medications. The following criteria were used successively to select the best model: (1) at least 5% of individuals per group [18]; (2) entropy ≥ 0.8 (implying less uncertainty in the classification) [77–79]; (3) highest proportion of individuals per group with posterior probability group ≥ 0.8 [78]; (4) lowest Bayesian information criterion (BIC) in absolute value [18]. To enhance the robustness of the trajectory modelling, growth mixture models were estimated using 100 initial starting values. This approach reduces the risk of convergence to local maxima and increases the likelihood of identifying the global maximum likelihood solution, thereby improving the stability and reproducibility of the trajectory groups [80]. See Supplementary Appendix 2 for modelling fit indices.

We described the profiles of trajectory groups using descriptive statistics, and performed comparative analyses using bivariable statistical testing (Chi-square tests with Tukey style multiple comparisons of proportions [81] and Kruskal-Wallis test with Dwass-Steel-Critchlow-Fligner test [82] for post-hoc pairwise analyses), with statistical significance defined as a p-value < 0.05. As the aim was not to identify causal or modifiable risk factors, but to describe real-world differences between groups, we opted for bivariate comparisons as opposed to multivariable analysis. Lastly, a Venn diagram illustrated the overlap between high risk individuals identified by the MQS-4.0 trajectory and those identified by the pain medication count trajectory [83].

The proportion of missing data across outcomes and compared variables was low (0–3.7%; see footnotes of Tables 2–4); all analyses were conducted on the available data without imputation. Growth mixture models for MQS-4.0 risk scores were estimated using the *hlme* function from the R package *lcmm* (R Core Team, Vienna, Austria), which is restricted to Gaussian outcomes [84]. Given the distributional properties of medication count data (non-negative integers with a skewed distribution), an alternative modelling approach appropriate for count-type outcomes was used (*FLXMRziglm* function from the R package *flexmix*). All other analyses were carried out with SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Sample

This study was conducted among 8,760 adults living with CP and covered by the public drug insurance plan during the two years following their participation in the Canadian Community Health Survey (Figure 1). Table 1 shows the

Table 2: Medications Used at the Time of Survey completion

Medication variables	Whole sample	Females	Males
Risk associated with pain-related medications according to the Medication Quantification Scale (MQS-4.0)			
Medication Quantification Scale (MQS-4.0) score –			
mean ± SD	8.7 ± 9.3	9.4 ± 9.4	7.4 ± 8.8
median (IQR)	6.0 (13.0)	8.0 (14.0)	5.0 (12.0)
Pain-related medications used (those considered in the calculation of the MQS-4.0)			
Number of different medications used –			
mean ± SD	1.4 ± 1.7	1.5 ± 1.7	1.2 ± 1.53
median (IQR)	1.0 (2.0)	1.0 (2.0)	1.0 (2.0)
≥ 2 medications – n (%)	3,275 (37.4)	2,341 (41.2)	934 (30.4)
≥ 5 medications – n (%)	485 (5.5)	354 (6.2)	131 (4.3)
≥ 10 medications – n (%)	<1%[a]	<1%[a]	<1%[a]
Medications used across all therapeutic indications			
Number of different medications used –			
mean ± SD	6.4 ± 5.1	6.9 ± 5.1	5.6 ± 5.0
Median (IQR)	6.0 (7.0)	6.0 (7.0)	5.0 (7.0)
≥ 5 medications – n (%)	5,180 (59.1)	3,577 (62.9)	1,603 (52.1)
≥ 10 medications – n (%)	2,152 (24.6)	1,552 (27.3)	600 (19.5)

IQR: Interquartile range. SD: Standard deviation. Proportion of missing data across presented variables: 0.0%. [a]When cell sizes are too small, the Institut de la statistique du Québec restricts data release for confidentiality reasons.

profile of the study sample. Table 2 shows baseline MQS-4.0 risk scores, the number of pain-related medications, and polypharmacy classifications (2 or more, 5 or more and 10 or more).

Trajectory Groups Obtained Using MQS-4.0 Risk Scores

When using the monthly MQS-4.0 scores to represent the risk associated with pain-related medications over the two-year follow-up period, GMM revealed that a linear four-group model best fitted the data (Figure 2): **(1)** 'low stable risk' group (n=2,988; 34.1% of the sample; the mean monthly risk score varied from 0.3±1.5 to 0.5±1.9 in this group); **(2)** 'moderate stable risk' group (n=4,469; 51.0% of the sample; the mean monthly risk score varied from 8.6±6.8 to 9.1±6.9 in this group); **(3)** 'increasing to high risk' group (n=654; 7.5% of the sample; the mean monthly risk increased from 9.7±9.9 to 18.7±10.1); **(4)** 'high risk decreasing' group (n=649; 7.4% of the sample; the mean monthly risk decreased from 18.3±10.8 to 10.8±11.0 over the two-year period).

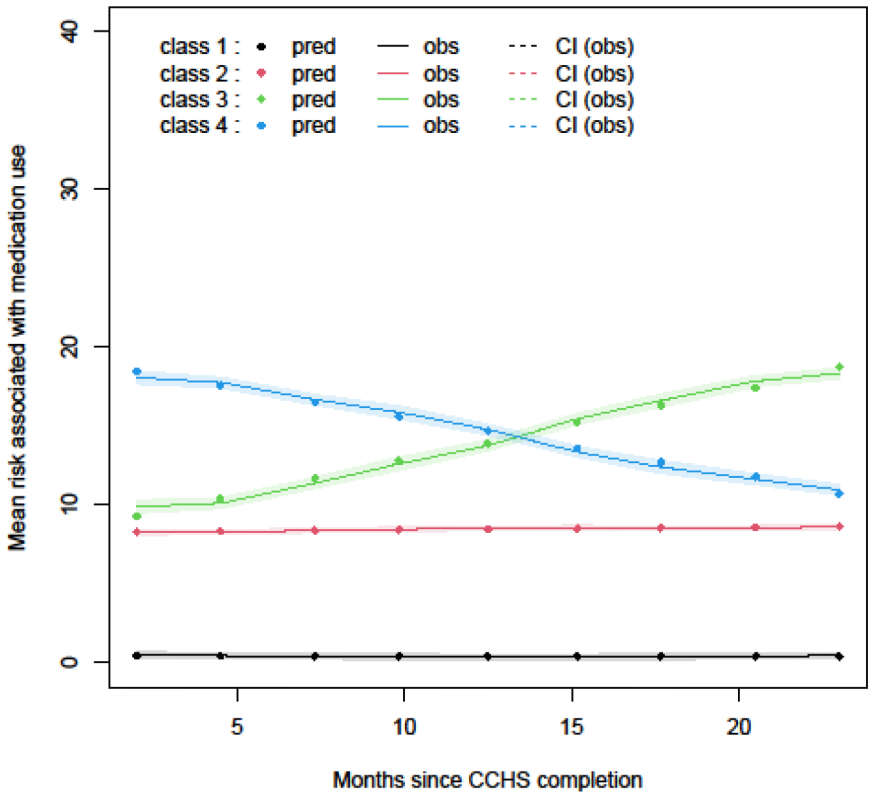
As shown in Table 3, the trajectory classification based on the MQS-4.0 risk scores allowed for the differentiation of sociodemographic characteristics, pain characteristics, health profiles, and healthcare utilisation. The participants of the 'increasing to high risk' group showed the highest proportion of the following characteristics: no secondary school diploma, residing in a remote region, number of different prescribers, general practitioner visits, emergency department visits, and episodes of hospitalisation. They also showed the highest prevalence of benzodiazepines and opioids use, and this group showed the highest prevalence of participants who died after the trajectory modelling period.

Trajectory Groups Obtained Using Medication Count

When using the monthly number of pain-related medications over the two-year follow-up period, GMM revealed that a five-group model best fitted the data (Figure 3): **(1)** 'zero pain-related medication' group (n=1,307; 14.9%; the mean number of pain-related medications used was 0.0±0.0); **(2)** 'occasional use of at least one pain-related medication' group (n=1,831; 20.9%; the mean number varied from 0.1±0.4 to 0.2±0.5); **(3)** 'low stable number of pain-related medications' group (n=2,750; 31.4%; 0.9±0.7 to 1.0±0.7); **(4)** 'moderate stable number of pain-related medications' group (n=2,137; 24.4%; 2.2 ± 1.0 to 2.4±1.0); **(5)** 'high number of pain-related medications' group (n=735; 8.4%; 4.5±1.5 to 4.7±1.4).

As shown in Table 4, trajectory classification based on the number of pain-related medications appeared less effective in differentiating sociodemographic characteristics, pain characteristics, health profiles, and healthcare utilisation. In fact, there were no differences between the five groups for most participant characteristics. Only the 'zero pain-related medication' group showed differences compared to all other trajectory groups.

Figure 2: Trajectory Groups Obtained Using MQS-4.0 Risk Scores



Black curve: 'low stable risk' group; Red curve: 'moderate stable risk' group; Green curve: 'increasing to high risk' group; Blue curve: 'high risk decreasing' group; Plain line: observed mean of risk associated with medication use. Dotted line: estimated mean of risk associated with medication use by the GMM. GMM: Growth Mixture Modelling. CCHS: Canadian Community Health Survey.

High Risk/High-Count Groups Identified by the Two Approaches

We analysed the overlaps between high risk/high-count individuals identified by the MQS-4.0 ('increasing to high risk' and 'high risk decreasing' groups) and those identified by medication count ('moderate stable' and 'high number of pain-related medications' groups) using a Venn diagram (Figure 4). While some overlap was observed, most trajectory groups did not match, suggesting that a higher medication count does not always indicate higher risk. Some individuals with fewer medications were at high risk. For instance, 872 (432 + 440) participants were exclusively in the high risk groups without being part of the higher medication count groups. These participants primarily used aspirin, pregabalin, oxycodone, clonazepam, and fentanyl. Conversely, 2,441 (1,813 +628) participants were exclusively in the moderate or high medication count groups without being in the high risk groups, with common medications including acetaminophen, amitriptyline, celecoxib, corticosteroid cream, and trazodone. Also, among individuals classified in high risk/low-count trajectories, the mean monthly number of medications ranged from 0.6 $\pm$ 0.7 to 0.7 $\pm$ 0.8, suggesting that elevated medication-related risk may occur even with relatively few medications. In contrast, among individuals classified in low-risk/high-count trajectories, the mean monthly number of medications ranged from 4.4 $\pm$ 1.4 to 4.7 $\pm$ 1.4.

Discussion

This study aimed to examine how a risk-based measure and a count-based measure may differently classify medication use trajectories in the real-world. We showed that both the MQS-4.0 risk score and medication count effectively created statistically robust (based on entropy and Bayesian information criterion) and clinically interpretable trajectory groups. However, MQS-4.0 was more discriminative in identifying differences in sociodemographic, pain, health, and healthcare characteristics. Our hypothesis was confirmed: higher medication count does not always equate to higher risk, and some individuals using fewer medications may be at higher risk. These findings suggest that composite risk scores may offer complementary value for subgroup analyses and personalised approaches in chronic pain research, depending on the intended research or clinical objective.

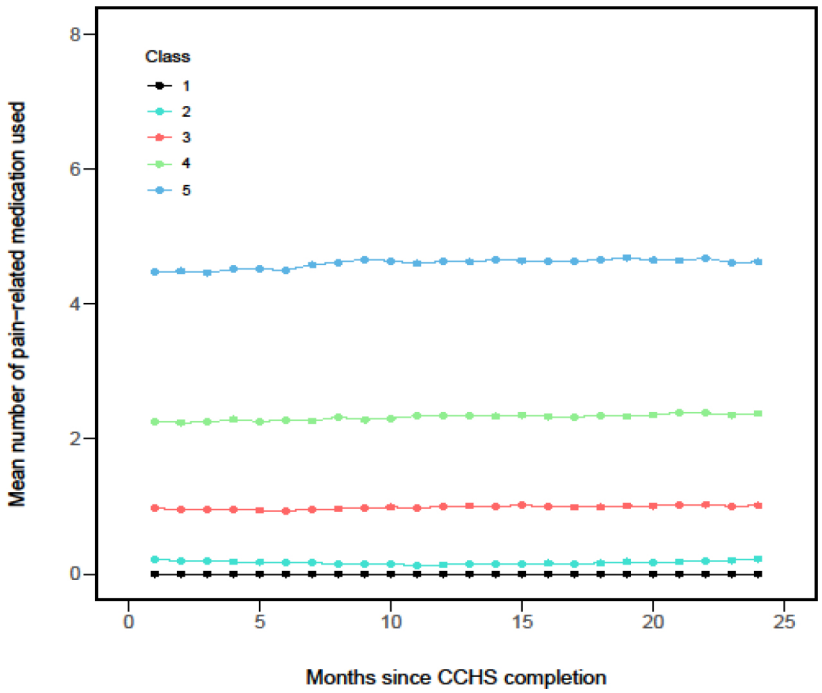
In our study, a higher number of pain-related medications did not automatically reflect increased risk levels. This supports the hypothesis underlying the justification for the use of the MQS-4.0 for CP populations [22]. Furthermore, this could be explained by the fact that certain medication classes are riskier than others [22]. For example, in a context

Table 3: Patient Characteristics According to Trajectory Group Membership Determined using MQS-4.0 Risk Scores

Population characteristics	Low stable risk 2,988 (34.1)	Moderate stable risk 4,469 (51.0)	Increasing to high risk 654 (7.5)	High risk decreasing 649 (7.4)	p-value[a]
Sociodemographic profile					
Age – n (%)[d]					
$<$ 65 years old	1,721 (57.6)	1,668 (37.3)	320 (48.9)	293 (45.2)	**$<$.0001**
$\geq$ 65 years old	1,267 (42.4)	2,801 (62.7)	334 (51.1)	356 (54.8)	
Sex – n (%)					
Female	1,774 (59.4)	3,021 (67.6)	443 (67.7)	446 (68.7)	**$<$.0001**
Male	1,214 (40.6)	1,448 (32.4)	211 (32.3)	203 (31.3)	
Education level – n (%)					
No secondary school diploma	926 (31.5)	2,064 (46.7)	327 (50.8)	283 (44.2)	**$<$.0001**
Secondary school diploma or more	2,012 (68.5)	2,355 (53.3)	317 (49.2)	357 (55.8)	
Relationship status – n (%)					
Not in a relationship	1,627 (54.5)	2,618 (58.6)	394 (60.2)	417 (64.3)	**$<$.0001**
In a relationship	1,359 (45.5)	1,848 (41.4)	260 (39.8)	232 (35.7)	
Annual household income (Can$) – n (%)					
$<$ 20,000	769 (25.7)	1,649 (39.9)	268 (41.0)	278 (42.8)	**$<$.0001**
$\geq$ 20,000	2,219 (74.3)	2,820 (60.1)	386 (59.0)	371 (57.2)	
Living in a remote region					
No	2,277 (76.2)	3,203 (71.7)	443 (67.7)	461 (71.0)	**$<$.0001**
Yes	711 (23.8)	1,266 (28.3)	211 (32.3)	188 (29.0)	
Pain symptoms					
Pain intensity – n (%)					
Mild	826 (27.9)	769 (17.4)	87 (13.4)	77 (12.0)	**$<$.0001**
Moderate/Severe	2,137 (72.1)	3,646 (82.6)	562 (86.6)	567 (88.0)	
Activities prevented by pain or discomfort – n (%)					
A few	2,309 (77.7)	2,918 (65.6)	338 (52.2)	317 (49.1)	**$<$.0001**
Some/Most	663 (22.31)	1,528 (34.4)	309 (47.8)	329 (50.9)	
General and mental health					
Self-perceived general health – n (%)					
Good/Very good/ Excellent	2,266 (76.0)	2,438 (54.6)	279 (42.8)	271 (41.8)	**$<$.0001**
Fair/Poor	717 (24.0)	2,024 (45.4)	373 (57.2)	377 (58.2)	
Self-perceived mental health – n (%)					
Good/Very good/ Excellent	2,689 (92.8)	3,788 (88.4)	527 (83.5)	506 (81.5)	**$<$.0001**
Fair/Poor	209 (7.2)	495 (11.6)	104 (16.5)	115 (18.5)	
Healthcare and medication profile					
Continuity of care[b] – mean $\pm$ SD	83.4$\pm$22.3	85.5$\pm$19.8	84.5$\pm$19.7	84.1$\pm$19.7	**0.0214**
Number of different prescribers[b] – mean $\pm$ SD	2.8$\pm$2.5	4.6$\pm$3.4	6.2$\pm$4.3	6.0$\pm$4.1	**$<$.0001**
Number of GP visits[b] – mean $\pm$ SD	4.5$\pm$4.8	7.6$\pm$6.1	9.8$\pm$8.1	9.1$\pm$7.7	**$<$.0001**
Number of specialist visits[b] – mean $\pm$ SD	5.3$\pm$8.7	9.1$\pm$13.2	12.4$\pm$16.9	11.4$\pm$11.4	**$<$.0001**
Number of ED visits[b] – mean $\pm$ SD	0.9$\pm$1.7	1.5$\pm$2.5	2.8$\pm$3.8	2.2$\pm$3.4	**$<$.0001**
Number of episodes of hospitalisation[b] – mean $\pm$ SD	0.3$\pm$0.7	0.6$\pm$1.1	1.1$\pm$1.4	1.0$\pm$1.5	**$<$.0001**
Polypharmacy (use of $\geq$2 medications for the same condition)[c] – n (%)					
No	2,876 (96.3)	2,165 (48.4)	288 (44.0)	156 (24.0)	**$<$.0001**
Yes	112 (3.7)	2,304 (51.6)	366 (56.0)	493 (76.0)	
Excessive polypharmacy (use of $\geq$ 10 all-cause medications)[c] – n (%)					
No	2,869 (96.0)	3,048 (68.2)	406 (62.1)	285 (43.9)	**$<$.0001**
Yes	119 (4.0)	1,421 (31.8)	248 (37.9)	364 (56.1)	
Use of benzodiazepines[b] – n (%)					
No	2,779 (93.0)	2,537 (56.8)	245 (37.5)	259 (39.9)	**$<$.0001**
Yes	209 (7.0)	1,932 (43.2)	409 (62.5)	390 (60.1)	
Use of opioids[b]– n (%)					
No	2,684 (89.8)	3,374 (75.5)	325 (49.7)	366 (56.4)	**$<$.0001**
Yes	304 (10.2)	1,095 (24.5)	329 (50.3)	283 (43.6)	
Mortality					
All-cause mortality – n (%)					
No	2,900 (97.1)	4,129 (92.4)	588 (89.9)	597 (92.0)	**$<$.0001**
Yes	88 (2.9)	340 (7.6)	66 (10.1)	52 (8.0)	

[a]Chi-square tests or Kruskal-Wallis tests with Tukey style multiple comparisons of proportions or Dwass-Steel-Critchlow-Fligner tests for post-hoc pairwise analyses. [b]Measured in the two years after survey completion. [c]Measured in the year before survey completion. Proportion of missing data across presented variable ranges between 0.0% and 3.7%. P-values $<$ 0.05 are highlighted in bold. [d]Age was dichotomised at 65 years, as most polypharmacy studies focus on older adults [85, 86].

Figure 3: Trajectories of pain-related medication use in the whole study sample



Black curve: 'zero pain-related medication' group; Turquoise curve: 'occasional use of at least one pain-related medication' group; Red curve: 'low stable number of pain-related medications' group; Green curve: 'moderate stable number of pain-related medications' group; Blue curve: 'high number of pain-related medications' group; Plain line: observed mean number of pain-related medications used; Dotted line: estimated mean number of pain-related medications used by the GMM. GMM: Growth Mixture Modelling. CCHS: Canadian Community Health Survey.

where opioid prescriptions are highly debated for CP [87, 88], rational polypharmacy potentially offers an alternative strategy by integrating non-opioid medications (meaning sometimes a higher number of lower risk medications). This dissociation underscores the limitation of relying solely on medication count as a proxy for the risk associated with medication use; medication count alone may lead to the under-identification of individuals vulnerable to adverse effects. A parallel can

Table 4: Patient Characteristics According to their Trajectory Group Membership Determined Using the Number of Pain-Related Medications

Population characteristics	**Zero pain-related medications 1,307 (14.9)**	**Occasional use of pain-related medications 1,831 (20.9)**	**Low stable number of pain-related medications 2,750 (31.4)**	**Moderate stable number of pain-related medications 2,137 (24.4)**	**High number of pain-related medications 735 (8.4)**	**p-value[a]**
Sociodemographic profile						
Age – n (%)						
< 65 years old	575 (44.0)	847 (46.3)	1,240 (45.1)	992 (46.4)	348 (47.4)	0.7009
≥ 65 years old	732 (56.0)	984 (53.7)	1,510 (54.9)	1,145 (53.6)	387 (52.6)	
Sex – n (%)						
Female	820 (62.7)	1,227 (67.0)	1,780 (64.7)	1,391 (65.1)	466 (63.4)	0.1328
Male	487 (37.3)	604 (33.0)	970 (35.3)	746 (34.9)	269 (36.6)	
Education level – n (%)						
No secondary school diploma	487 (38.1)	773 (42.8)	1,154 (42.5)	890 (42.1)	296 (40.7)	**0.0006**
Secondary school diploma or more	792 (61.9)	1,034 (57.2)	1,561 (57.5)	1,223 (57.9)	431 (59.3)	
Relationship status – n (%)						
Not in a relationship	749 (57.3)	1,070 (58.5)	1,558 (56.7)	1,248 (58.4)	431 (58.9)	0.6360
In a relationship	558 (42.7)	760 (41.5)	1,191 (43.3)	889 (41.6)	301 (41.1)	
Annual household income (Can$) – n (%)						
< 20,000	377 (28.8)	657 (35.9)	945 (34.4)	735 (34.4)	250 (34.0)	**<.0001**
≥ 20,000	930 (71.2)	1,174 (64.1)	1,805 (65.6)	1,402 (65.6)	485 (66.0)	

Continued

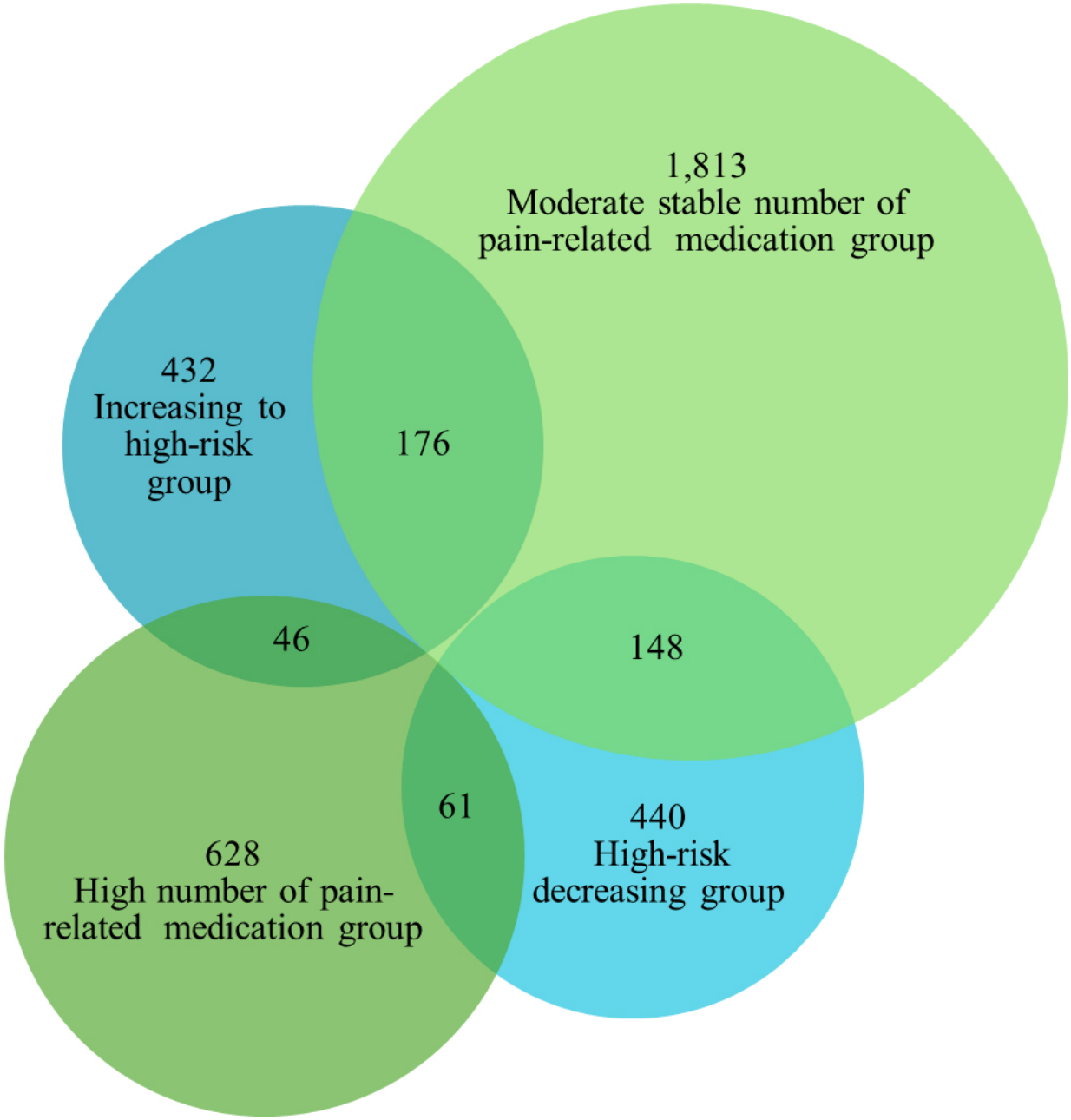
Table 4: Continued

Population characteristics	Zero pain-related medications	Occasional use of pain-related medications	Low stable number of pain-related medications	Moderate stable number of pain-related medications	High number of pain-related medications	p-value[a]
Living in a remote region						
No	960 (73.5)	1,327 (72.5)	2,019 (73.4)	1,546 (72.3)	532 (72.4)	**0.0116**
Yes	347 (26.5)	504 (27.5)	731 (26.6)	591 (27.7)	203 (27.6)	
Pain symptoms						
Pain intensity – n (%)						
Mild	254 (19.6)	372 (20.6)	542 (19.9)	438 (20.7)	153 (21.1)	0.8819
Moderate/Severe	1,042 (80.4)	1,438 (79.4)	2,180 (80.1)	1,678 (79.3)	574 (78.9)	
Activities prevented by pain or discomfort – n (%)						
A few	913 (70.2)	1,215 (66.8)	1,845 (67.5)	1,418 (66.8)	491 (66.9)	0.2566
Some/Most	388 (29.8)	604 (33.2)	888 (32.5)	706 (33.2)	243 (33.1)	
General and mental health						
Self-perceived general health – n (%)						
Good/Very good/ Excellent	808 (61.9)	1,071 (58.6)	1,625 (59.2)	1,307 (61.2)	443 (60.4)	0.2539
Fair/Poor	498 (38.1)	756 (41.4)	1,118 (40.8)	828 (38.8)	291 (39.6)	
Self-perceived mental health – n (%)						
Good/Very good/ Excellent	1,103 (88.7)	1,581 (89.1)	2,343 (88.7)	1,833 (89.1)	650 (90.8)	0.5962
Fair/Poor	141 (11.3)	193 (10.9)	299 (11.3)	224 (10.9)	66 (9.2)	
Healthcare and medication profile						
Continuity of care[b] – mean ± SD	84.0±20.5	83.9±21.0	85.2±20.4	84.7±20.7	85.6±20.6	**0.0470**
Number of different prescribers[b] – mean ± SD	4.43±3.7	4.3±3.6	4.2±3.4	4.2±3.4	4.1±3.3	0.5699
Number of GP visits[b] – mean ± SD	6.4±5.8	7.2±6.2	7.0±6.7	6.6±5.9	6.9±6.4	**0.0029**
Number of specialist visits[b] – mean ± SD	8.5±10.6	8.3±12.0	8.1±11.2	8.3±15.2	8.1±9.6	0.8195
Number of ED visits[b] – mean ± SD	1.3±2.3	1.5±2.6	1.6±2.8	1.4±2.4	1.4±2.5	**0.0396**
Number of episodes of hospitalisation[b] – mean ± SD	0.5±1.0	0.6±1.1	0.6±1.1	0.6±1.1	0.6±1.1	0.2478
Polypharmacy (use of ≥2 medications for the same condition)[c] – n (%)						
No	1,307 (100.0)	1,023 (55.9)	1,557 (56.6)	1,188 (55.6)	410 (55.8)	**<.0001**
Yes	0 (0.0)	808 (44.1)	1,193 (43.4)	949 (44.4)	325 (44.2)	
Excessive polypharmacy (use of ≥ 10 all-cause medications)[c]– n (%)						
No	980 (75.0)	1,362 (74.4)	2,075 (75.5)	1,644 (76.9)	547 (74.4)	0.3771
Yes	327 (25.0)	469 (25.6)	675 (24.5)	493 (23.1)	188 (25.6)	
Use of benzodiazepines[b] – n (%)						
No	1,307 (100.0)	1,081 (59.0)	1,670 (60.7)	1,306 (61.1)	456 (62.0)	**<.0001**
Yes	0 (0.0)	750 (41.0)	1,080 (39.3)	831 (38.9)	279 (38.0)	
Use of opioids[c] – n (%)						
No	1,307 (100.0)	1,353 (73.9)	1,998 (72.7)	1,551 (72.6)	540 (73.5)	**<.0001**
Yes	0 (0.0)	478 (26.1)	752 (27.3)	586 (27.4)	195 (26.5)	
Mortality						
All-cause mortality – n (%)						
No	1,286 (98.4)	1,708 (93.3)	2,551 (92.8)	1,981 (92.7)	688 (93.6)	**<.0001**
Yes	21 (1.6)	123 (6.7)	199 (7.2)	156 (7.3)	47 (6.4)	

[a]Chi-square tests or Kruskal-Wallis tests with Tukey style multiple comparisons of proportions or Dwass-Steel-Critchlow-Fligner tests for post-hoc pairwise analyses. [b]Measured in the two years after survey completion. [c]Measured in the year before survey completion. Proportion of missing data across presented variable ranges between 0% and 3.7%. P-values < 0.05 are highlighted in bold.

be drawn here with studies outside the field of pain which have demonstrated the value of composite medication scores [89, 90]. However, although the MQS-4.0 has demonstrated validity across multiple versions and its various iterations have been widely used in CP research, its weighting system is based on healthcare professionals' perceptions of medication-related risk rather than solely on pharmacological potency, which may result in similar detriment weights for medications with different clinical risk profiles. In addition, the MQS-4.0 does not explicitly account for dose quantity beyond medication subclasses. The limited overlap between medication count and medication-related risk classifications may suggest that these

Figure 4: Overlap between the high risk/high-count individuals identified through the MQS-4.0 risk score trajectory analysis versus the trajectory analysis based on the number of pain-related medications



approaches capture distinct but complementary dimensions of medication use patterns, although we cannot exclude the possibility that some of the observed discordance may reflect methodological artefacts.

In terms of health inequalities, the trajectory groups obtained through MQS-4.0 risk score analysis are more discriminative than those obtained using pain-related medication count trajectory analysis. While differences in modelling approaches may contribute to some variation in the identified trajectories, the extent to which the observed differences are attributable to the underlying constructs, their distributions, or the modelling approaches themselves remains uncertain and distributions of the underlying measures. Nevertheless, MQS-4.0 risk score trajectory groups showed clearer differences in sociodemographic profiles, pain characteristics, general and mental health, healthcare utilisation, and even all-cause mortality. To our knowledge, no other study has compared, in this way, a medication risk score to the number of medications used.

Our study reinforces existing evidence supporting the value of risk-based approaches over count-based approaches in the study of medication use for CP. Our results support the use of such a tool to identify high risk subgroups, even among individuals with fewer medications, to achieve greater granularity in understanding medication-related risks. This is especially critical in CP research, where polypharmacy [8] and high risk medications like benzodiazepines and opioids are prevalent [91]. Allowing risk trajectory differentiation, the MQS-4.0 enables relevant exploration of medication use patterns that can present a hazard and their impact on patient

outcomes. Furthermore, the observed differences in risk profiles highlight opportunities for researchers to investigate tailored interventions that could improve safety among individuals living with CP.

Strengths and Limitations

This study used data from the TorSaDE Cohort, a unique probability-based longitudinal database with very few missing data. Its large, diverse community sample enhances external validity compared to pain research focused on tertiary care settings. The survey data also provides key covariates for integrating health administrative databases, the most valid way to study healthcare use and medication prescribing [92, 93]. However, limitations of our study include the definition of CP used in this study that differs from the traditional definitions. While some studies have shown this definition yields comparable results in terms of prevalence estimates [33, 35, 36, 46], the possibility of misclassification cannot be excluded. Moreover, the drug insurance claims data used in this study captures only community-acquired prescriptions, excluding over-the-counter and hospital medications. Additionally, Québec's drug insurance data primarily covers lower socioeconomic groups; this affects the generalizability of the study [94]. Regarding groups profiles, the comparisons across trajectory groups were bivariate and aimed at evaluating the extent to which trajectory classifications derived from each approach captured sociodemographic and clinical differences between individuals. These analyses were not designed to identify independent factors associated with trajectory membership, and therefore no multivariable adjustment was performed. Future studies could build on these findings by using multivariable approaches to further examine factors independently associated with trajectory membership and to better understand modifiable factors underlying different medication risk profiles.

Conclusion

While both the MQS-4.0 risk scores and the medication count approaches generated statistically robust and clinically interpretable trajectory groups, the MQS-4.0 risk score captured more meaningful distinctions in terms of sociodemographic and clinical variables. Our study also highlighted that higher medication use does not necessarily indicate greater risk, as individuals with fewer medications can still present significant risk. Our findings highlight the potential value of combining composite risk scores and medication count measures when studying medication use among individuals living with chronic pain, as these approaches appear to capture different aspects of medication-related burden and may provide complementary value for subgroup analyses and personalised approaches in chronic pain research, depending on the intended research or clinical purpose.

Acknowledgements

We thank Emily-Jayn Rubec, who provided professional linguistic revision services when revising our paper. We would also like to thank Oumar Mallé Samb, Gabriel Gingras-Lacroix, and Joséanne Desrosiers, close collaborators on the qualitative phase of the larger project within which the present analysis is situated. We would also like to thank the members of the TorSaDE Cohort Working Group for sharing their methodologies and statistical expertise, which facilitated this project. The results reported herein correspond to the specific aims of grant number PJT 178216 awarded to principal investigator AL by the Canadian Institutes of Health Research (CIHR). HLNN, first author, is the recipient of *Fonds de recherche du Québec – secteur Santé* (FRQS) and Canadian Institutes of Health Research (CIHR) doctoral scholarships. The funders had no role in the design of the study, data collection, analysis, interpretation of data, or writing of the manuscript.

Statement on Conflicts of Interest

The authors have no conflicts of interest with any financial organisation regarding the material discussed in the manuscript.

Ethics Statement

Canadian Community Health Survey participants gave informed consent to Statistics Canada for the linkage of their responses to provincial health administrative databases and use for research purposes when they take part in the survey. De-identified data from the TorSaDE Cohort was accessed via the secure server of the *Institut de la statistique du Québec* (ISQ), which acts as the mandated data access authority. Ethical approval was obtained from the Commission d'accès à l'information du Québec (#1013990), Institut de la statistique du Québec (ISQ), and relevant university Research Ethics Boards (Université du Québec en Abitibi-Témiscamingue: #2018-02-Lacasse, A.; Centre hospitalier universitaire de Sherbrooke (CHUS): #2017-1504).

Data Availability Statement

Our dataset, the TorSaDE Cohort data that links Statistics Canada's Canadian Community Health Survey (CCHS) data and Québec Health Ministry data, is not publicly available. Access must be granted by the Institut de la statistique du Québec (ISQ). Programming codes can be obtained directly from the corresponding author.

Authors Contributions

AL, MGP, LG, and CH conceptualised the project and secured funding in collaboration with two patient partners (NM and SB). HLNN conducted the statistical analysis and drafted the manuscript in the context of her doctoral training supervised by AL. All authors critically revised the manuscript, gave final approval of the version to be published, and agreed to act as guarantors of the work.

AI in the Writing Process

During the preparation of this work the authors used ChatGPT version 4.o in order to assist with the linguistic revision as authors are French speakers. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

1. Moore, R.A., et al., *The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain.* Pain Pract, 2014. **14**(1): p. 79-94. https://doi.org/10.1111/papr.12050

2. Rometsch, C., et al., *Chronic pain in European adult populations: a systematic review of prevalence and associated clinical features.* PAIN, 2025. **166**(4). https://doi.org/10.1097/j.pain.0000000000003406

3. Treede, R.-D., et al., *A classification of chronic pain for ICD-11.* Pain, 2015. **156**(6): p. 1003-1007. https://doi.org/10.1097/j.pain.0000000000000160

4. Campbell, F., M. Hudspith, and M. Choinière, *La douleur chronique au Canada: jeter les bases d'un programme d'action.* Rapport du groupe de travail canadien sur la douleur, 2019.

5. Sirois, C., et al., *Polypharmacy definitions for multimorbid older adults need stronger foundations to guide research, clinical practice and public health.* Pharmacy, 2019. **7**(3): p. 126. https://doi.org/10.3390/pharmacy7030126

6. Ferrari, A., et al., *Polypharmacy among headache patients: a cross-sectional study.* CNS drugs, 2018. **32**(6): p. 567-578. https://doi.org/10.1007/s40263-018-0522-8

7. Giummarra, M.J., et al., *Polypharmacy and chronic pain: harm exposure is not all about the opioids.* Pain Medicine, 2015. **16**(3): p. 472-479. https://doi.org/10.1111/pme.12586

8. Zahlan, G., et al., *Polypharmacy and Excessive Polypharmacy Among Persons Living with Chronic Pain: A Cross-Sectional Study on the Prevalence and Associated Factors.* Journal of Pain Research, 2023: p. 3085-3100. https://doi.org/10.2147/JPR.S411451

9. Chang, T.I., et al., *Polypharmacy, hospitalization, and mortality risk: A nationwide cohort study.* Scientific reports, 2020. **10**(1): p. 1-9. https://doi.org/10.1038/s41598-020-75888-8

10. Shi, S., K. Mörike, and U. Klotz, *The clinical implications of ageing for rational drug therapy.* Eur J Clin Pharmacol, 2008. **64**(2): p. 183-99. https://doi.org/10.1007/s00228-007-0422-1

11. Nunnari, P., et al., *Prescribing cascades and medications most frequently involved in pain therapy: a review.* Eur Rev Med Pharmacol Sci, 2021. **25**(2): p. 1034-1041. https://doi.org/10.26355/eurrev_202101_24673

12. Palapinyo, S., J. Methaneethorn, and N. Leelakanok, *Association between polypharmacy and depression: a systematic review and meta-analysis.* Journal of Pharmacy Practice and Research, 2021. **51**(4): p. 280-299. https://doi.org/10.1002/jppr.1749

13. Schenker, Y., et al., *Associations Between Polypharmacy, Symptom Burden, and Quality of Life in Patients with Advanced, Life-Limiting Illness.* J Gen Intern Med, 2019. **34**(4): p. 559-566. https://doi.org/10.1007/s11606-019-04837-7

14. Leelakanok, N., et al., *Association between polypharmacy and death: A systematic review and meta-analysis.* J Am Pharm Assoc (2003), 2017. **57**(6): p. 729-738.e10. https://doi.org/10.1016/j.japh.2017.06.002

15. Gosselin, M., et al., *Classifying Polypharmacy According to Pharmacotherapeutic and Clinical Risks in Older Adults: A Latent Class Analysis in Quebec, Canada.* Drugs Aging, 2023. **40**(6): p. 573-583. https://doi.org/10.1007/s40266-023-01028-2

16. Chou, R., et al., *Opioid treatments for chronic pain.* 2020.

17. McDonagh, M.S., et al., *Nonopioid pharmacologic treatments for chronic pain.* 2020.

18. Nguena Nguefack, H.L., et al., *Trajectory modelling techniques useful to epidemiological research: a comparative narrative review of approaches.* Clinical epidemiology, 2020: p. 1205-1222. https://doi.org/10.2147/CLEP.S265287

19. Harden, R.N., et al., *Medication Quantification Scale Version III: update in medication classes and revised detriment weights by survey of American Pain Society Physicians.* The Journal of Pain, 2005. **6**(6): p. 364-371. https://doi.org/10.1016/j.jpain.2005.01.350

20. Kee, W., S. Steedman, and S. Middaugh, *Medication quantification scale (MQS): update of detriment weights and medication additions.* Am J Pain Management, 1998. **8**: p. 83-8.

21. Masters Steedman, S., et al., *Chronic-pain medications: equivalence levels and method of quantifying usage.* Clin J Pain, 1992. **8**(3): p. 204-14.

22. De Clifford-Faugère, G., et al., *The Medication Quantification Scale 4.0: An Updated Index Based on Prescribers' Perceptions of the Risk Associated With Chronic Pain Medications.* The Journal of Pain, 2023. https://doi.org/10.1016/j.jpain.2023.09.010

23. Karla J. Stormo, K.J., et al., *Medication quantification scores and evaluation of patient pharmacology profiles.* Current Review of Pain, 1998. **2**(3): p. 171–174. https://doi.org/10.1007/s11916-998-0015-4

24. Gallizzi, M., et al., *Medication Quantification Scale Version III: internal validation of detriment weights using a chronic pain population.* Pain Pract, 2008. **8**(1): p. 1-4. https://doi.org/10.1111/j.1533-2500.2007.00163.x

25. Gallizzi, M.A., et al., *Use of a medication quantification scale for comparison of pain medication usage in patients with complex regional pain syndrome (CRPS).* Pain Med, 2015. **16**(3): p. 494-500. https://doi.org/10.1111/pme.12549

26. Vanasse, A., et al., *Cohort profile: the care trajectories—enriched data (TorSaDE) cohort.* International journal of epidemiology, 2021. **50**(4): p. 1066-1066h. https://doi.org/10.1093/ije/dyaa167

27. Statistics Canada. *Canadian Community Health Survey - Annual Component (CCHS) - Detailed information for 2012.* 2012 [cited 2017 April, 15th]; Available from: http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=135927.

28. Régie de l'assurance maladie du Québec. *La RAMQ en quelques chiffres.* 2025 [cited 2025 January 30]; Available from: https://www.ramq.gouv.qc.ca/fr/donnees-statistiques/ramq-quelques-chiffres.

29. Lacasse, A., et al., *Chronic pain patients' willingness to share personal identifiers on the web for the linkage of medico-administrative claims and patient-reported data: the chronic pain treatment cohort.* Pharmacoepidemiology and drug safety, 2021. **30**(8): p. 1012-1026. https://doi.org/10.1002/pds.5255

30. Nguena Nguefack, H.L., et al., *Distinct care trajectories among persons living with arthritic conditions: A two-year state sequence analysis.* Frontiers in Pain Research, 2022. **3**. https://doi.org/10.3389/fpain.2022.1014793

31. Tamblyn, R., et al., *The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec.* Journal of clinical epidemiology, 1995. **48**(8): p. 999-1009. https://doi.org/ 10.1016/0895-4356(94)00234-h

32. Andrew, R., et al., *The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain.* Pain Practice, 2014. **14**(1): p. 79-94. https://doi.org/10.1111/papr.12050

33. Reitsma, M., et al., *The epidemiology of chronic pain in Canadian men and women between 1994 and 2007: longitudinal results of the National Population Health Survey.* Pain Res Manag, 2012. **17**(3): p. 166-72. https://doi.org/10.1155/2012/875924

34. Ramage-Morin, P.L. and H. Gilmour, *Chronic pain at ages 12 to 44.* Health Rep, 2010. **21**(4): p. 53-61.

35. Reitsma, M.L., et al., *The prevalence of chronic pain and pain-related interference in the Canadian population from 1994 to 2008.* Chronic Dis Inj Can, 2011. **31**(4): p. 157-64.

36. Gilmour, H., *Chronic pain, activity restriction and flourishing mental health.* Health Rep, 2015. **26**(1): p. 15-22.

37. Ramage-Morin, P.L., *Chronic pain in Canadian seniors.* Health Rep, 2008. **19**(1): p. 37-52.

38. Hogan, M.E., et al., *Health utilities in people with chronic pain using a population-level survey and linked health care administrative data.* Pain, 2017. **158**(3): p. 408-416. https://doi.org/10.1097/j.pain.0000000000000776

39. Hogan, M.E., et al., *Incremental health care costs for chronic pain in Ontario, Canada: a population-based matched cohort study of adolescents and adults using administrative data.* Pain, 2016. **157**(8): p. 1626-33. https://doi.org/10.1097/j.pain.0000000000000561

40. Csupak, B., et al., *A population-based examination of the co-occurrence and functional correlates of chronic pain and generalized anxiety disorder.* J Anxiety Disord, 2018. **56**: p. 74-80. https://doi.org/10.1016/j.janxdis.2018.04.005

41. Grocott, B., J.L. Sommer, and R. El-Gabalawy, *Usual presence and intensity of pain are differentially associated with suicidality across chronic pain conditions: A population-based study.* J Psychosom Res, 2021. **148**: p. 110557. https://doi.org/10.1016/j.jpsychores.2021.110557

42. Liu, L.J.W., et al., *A Population Study of Prescribed Opioid-based Pain Reliever Use among Individuals with Mood and Anxiety Disorders in Canada.* Drug Alcohol Depend, 2020. **216**: p. 108229. https://doi.org/10.1016/j.drugalcdep.2020.108229

43. Men, F., et al., *Food insecurity, chronic pain, and use of prescription opioids.* SSM Popul Health, 2021. **14**: p. 100768. https://doi.org/10.1016/j.ssmph.2021.100768

44. Qadeer, R.A., L. Shanahan, and M.A. Ferro, *Chronic disruptive pain in emerging adults with and without chronic health conditions and the moderating role of psychiatric disorders: Evidence from a population-based cross-sectional survey in Canada.* Scand J Pain, 2017. **17**: p. 30-36. https://doi.org/10.1016/j.sjpain.2017.07.009

45. Roy, R., et al., *Understanding correlates of suicidality among those with usual pain and discomfort: A Canadian nationally representative study.* J Psychosom Res, 2021. **151**: p. 110651. https://doi.org/10.1016/j.jpsychores.2021.110651

46. Shupler, M.S., et al., *Pan-Canadian Estimates of Chronic Pain Prevalence From 2000 to 2014: A Repeated Cross-Sectional Survey Analysis.* J Pain, 2019. **20**(5): p. 557-565. https://doi.org/10.1016/j.jpain.2018.10.010

47. Sommer, J.L., C. Blaney, and R. El-Gabalawy, *A population-based examination of suicidality in comorbid generalized anxiety disorder and chronic pain.* J Affect Disord, 2019. **257**: p. 562-567. https://doi.org/10.1016/j.jad.2019.07.016

48. Su, Y., X. Meng, and C. D'Arcy, *Does Gender Moderate the Relationship Between Chronic Pain and Substance*

Use Disorder? Insights From a National Canadian Population Survey. Front Psychiatry, 2022. **13**: p. 799655. https://doi.org/10.3389/fpsyt.2022.799655

49. Farhadi, K., et al., *The effectiveness of wet-cupping for nonspecific low back pain in Iran: a randomized controlled trial.* Complement Ther Med, 2009. **17**(1): p. 9-15. https://doi.org/10.1016/j.ctim.2008.05.003

50. Guck, T.P., et al., *Predictive validity of the pain and impairment relationship scale in a chronic nonmalignant pain population.* Arch Phys Med Rehabil, 1999. **80**(1): p. 91-5. https://doi.org/10.1016/s0003-9993(99)90313-1

51. Jacob, E., et al., *Quantification of analgesic use in children with sickle cell disease.* Clin J Pain, 2007. **23**(1): p. 8-14. https://doi.org/10.1097/01.ajp.0000210938.58439.dd

52. Levesque, A., et al., *Use of High-Concentration Capsaicin Patch for the Treatment of Pelvic Pain: Observational Study of 60 Inpatients.* Pain Physician, 2017. **20**(1): p. e161-e167.

53. McCormick, Z.L., et al., *A Prospective Randomized Comparative Trial of Targeted Steroid Injection Via Epidural Catheter Versus Standard C7-T1 Interlaminar Approach for the Treatment of Unilateral Cervical Radicular Pain.* Reg Anesth Pain Med, 2017. **42**(1): p. 82-89. https://doi.org/10.1097/AAP.0000000000000521

54. Nguyen, J.P., et al., *Treatment of refractory headache secondary to intracranial endovascular procedure by transcutaneous electrical nerve stimulation of the occipital nerve.* Neurophysiol Clin, 2018. https://doi.org/10.1016/j.neucli.2018.05.041

55. Goudman, L., et al., *Cross-Country Differences in Pain Medication Before and After Spinal Cord Stimulation: A Pooled Analysis of Individual Patient Data From Two Prospective Studies in the United Kingdom and Belgium.* Neuromodulation, 2023. **26**(1): p. 215-223. https://doi.org/10.1111/ner.13524

56. Kwon, H.J., et al., *Comparison of Adjuvant Hypertonic Saline and Normal Saline for Epidural Block in Patients with Postherpetic Neuralgia: A Double-Blind, Randomized Trial.* Pain Res Manag, 2022. **2022**: p. 8081443. https://doi.org/10.1155/2022/8081443

57. Chae, J.S., W.J. Kim, and M.J. Jue, *Facet Joint Versus Transforaminal Epidural Steroid Injections in Patients With Cervical Radicular Pain due to Foraminal Stenosis: A Retrospective Comparative Study.* J Korean Med Sci, 2022. **37**(25): p. e208. https://doi.org/10.3346/jkms.2022.37.e208

58. Sim, J.H., et al., *Effectiveness of Epidural Balloon Neuroplasty in Patients With Chronic Spinal Stenosis Accompanied by Redundant Nerve Roots: A Longitudinal Cohort Study.* Pain Physician, 2022. **25**(6): p. e841-e850.

59. Bian, J., et al., *A Retrospective Comparison of Low-Temperature Plasma Ablation and Radiofrequency Thermocoagulation of the Thoracic Nerve Root for Refractory Postherpetic Neuralgia.* Pain Physician, 2024. **27**(4): p. 243-251.

60. Cheney, C.W., et al., *Cooled radiofrequency ablation for the treatment of refractory postamputation neuroma-associated pain: A prospective pilot study.* Pm r, 2026. **18**(1): p. 15-23. https://doi.org/10.1002/pmrj.13412

61. De Clifford-Faugère, G., et al., *Physicians' and patients' perceived risks of chronic pain medication and co-medications in Quebec, Canada: a cross-sectional study.* BMC Prim Care, 2025. **26**(1): p. 8. https://doi.org/10.1186/s12875-025-02704-5

62. Elango, Y., et al., *Comparison of the analgesic efficacy of intra-articular steroid injections and its combination with suprascapular nerve block for adhesive capsulitis of the shoulder joint: a randomized clinical trial.* Reg Anesth Pain Med, 2026. **51**(4): p. 404-410. https://doi.org/10.1136/rapm-2024-105902

63. Kim, C.S., et al., *Effects of Pulsed Radiofrequency Duration in Patients With Chronic Lumbosacral Radicular Pain: A Randomized Double-Blind Study.* Neuromodulation, 2025. **28**(2): p. 256-262. https://doi.org/10.1016/j.neurom.2024.03.006

64. Kumar, A., et al., *Ultrasound-guided pulsed radiofrequency ablation of stellate ganglion in upper-extremity phantom limb pain: a case series.* Anesth Pain Med (Seoul), 2024. **19**(4): p. 349-352. https://doi.org/10.17085/apm.24035

65. Liao, C., et al., *Ultra-Long-Term Real-World Outcomes of Lower Extremity Nerve Decompression for Painful Diabetic Peripheral Neuropathy: A Retrospective Cohort Study.* Neurol Ther, 2026. **15**(3): p. 1155-1175. https://doi.org/10.1007/s40120-026-00913-3

66. Lu, D., et al., *High Burden and Phenotype-Specific Variability of Pain Polypharmacy in Early Autoimmune Rheumatic Diseases: A 15-Year Real-World Analysis.* Res Sq, 2026. https://doi.org/10.21203/rs.3.rs-9152435/v1

67. Mohanty, A.J., et al., *Prophylactic Regenerative Peripheral Nerve Interface Surgery in Pediatric Lower Limb Amputation Patients.* Ann Surg, 2025. **282**(2): p. 346-351. https://doi.org/10.1097/SLA.0000000000006327

68. Parks, T., et al., *Exploring the impact of Namaste Care for individuals with advanced dementia: a systematic review of costs, effects and benefits.* BMJ Open, 2026. **16**(5): p. e102899. https://doi.org/10.1136/bmjopen-2025-102899

69. Ravaillault, S., et al., *Occipital Nerve Stimulation for Refractory Occipital Neuralgia: A Multicenter, Randomized, Controlled Trial [StimO Study].* J Clin Med, 2026. **15**(5). https://doi.org/10.3390/jcm15051922

70. Yildiz, G. and O.T. Akkaya, *A Comparison Between the Efficacy of Trigeminal Ganglion Radiofrequency*

Thermocoagulation and Ultrasound-Guided Maxillary-Mandibular Nerve Pulsed Radiofrequency in the Treatment of Trigeminal Neuralgia: A Randomized Clinical Trial. Cureus, 2024. **16**(6): p. e61565. https://doi.org/10.7759/cureus.61565

71. Yildiz, G., et al., *Comparison of Selective Nerve Root Pulsed Radiofrequency Vs Paramedian Interlaminar Epidural Steroid Injection for the Treatment of Painful Cervical Radiculopathy.* Pain Physician, 2024. **27**(2): p. E221-e229.

72. Leckman-Westin, E., et al., *Validation of a claims-based antipsychotic polypharmacy measure.* Pharmacoepidemiology and drug safety, 2014. **23**(6): p. 628-635. https://doi.org/10.1002/pds.3609

73. Hovstadius, B. and G. Petersson, *Factors leading to excessive polypharmacy.* Clinics in geriatric medicine, 2012. **28**(2): p. 159-172. https://doi.org/10.1016/j.cger.2012.01.001

74. Kingsbury, S.J., D. Yi, and G.M. Simpson, *Psychopharmacology: rational and irrational polypharmacy.* Psychiatric Services, 2001. **52**(8): p. 1033-1036. https://doi.org/10.1176/appi.ps.52.8.1033

75. Jee, S.H. and M.D. Cabana, *Indices for Continuity of Care: A Systematic Review of the Literature.* Medical Care Research and Review, 2006. **63**(2): p. 158-188. https://doi.org/10.1177/1077558705285294

76. Peters, S.A. and M. Woodward, *A roadmap for sex-and gender-disaggregated health research.* BMC medicine, 2023. **21**(1): p. 354. https://doi.org/10.1177/1077558705285294

77. Muthén, B., *Latent variable analysis: Growth mixture modeling and related techniques for longitudinal data.*, in *Handbook of quantitative methodology for the social sciences*, D. Kaplan, Editor. 2004, CA: Sage: Newbury Park. p. 345-368.

78. van der Nest, G., et al., *An overview of mixture modelling for latent evolutions in longitudinal data: Modelling approaches, fit statistics and software.* Advances in Life Course Research, 2020. **43**: p. 100323. https://doi.org/10.1016/j.alcr.2019.100323

79. Ram, N. and K.J. Grimm, *Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups.* International Journal of Behavioral Development, 2009. **33**(6): p. 565-576. https://doi.org/10.1177/0165025409343765

80. Hipp, J.R. and D.J. Bauer, *Local solutions in the estimation of growth mixture models.* Psychological methods, 2006. **11**(1): p. 36. https://doi.org/10.1037/1082-989X.11.1.36

81. Elliott, A.C. and J.S. Reisch, *Implementing a multiple comparison test for proportions in a 2xc crosstabulation in SAS®.* Proceedings of the SAS User's Group International, 2006. **31**: p. 204-231.

82. Elliott, A.C. and L.S. Hynan, *A SAS® macro implementation of a multiple comparison post hoc test for a Kruskal–Wallis analysis.* Computer methods and programs in biomedicine, 2011. **102**(1): p. 75-80. https://doi.org/10.1016/j.cmpb.2010.11.002

83. Ho, S.Y., et al., *What can Venn diagrams teach us about doing data science better?* International Journal of Data Science and Analytics, 2021. **11**(1): p. 1-10. https://doi.org/10.1007/s41060-020-00230-4

84. Proust-Lima, C., et al., *Package 'lcmm'.* CRAN R, 2016.

85. Kurczewska-Michalak, M., et al., *Polypharmacy Management in the Older Adults: A Scoping Review of Available Interventions.* Front Pharmacol, 2021. **12**: p. 734045. https://doi.org/10.3389/fphar.2021.734045

86. Keller, M.S., et al., *Cumulative Update of a Systematic Overview Evaluating Interventions Addressing Polypharmacy.* JAMA Network Open, 2024. **7**(1): p. e2350963-e2350963. https://doi.org/10.1001/jamanetworkopen.2023.50963

87. A. Morrone, L., et al., *Opioids resistance in chronic pain management.* Current neuropharmacology, 2017. **15**(3): p. 444-456. https://doi.org/10.2174/1570159X14666161101092822

88. Volkow, N., H. Benveniste, and A.T. McLellan, *Use and misuse of opioids in chronic pain.* Annual review of medicine, 2018. **69**(1): p. 451-465. https://doi.org/10.1146/annurev-med-011817-044739

89. Häppölä, P., et al., *A data-driven medication score predicts 10-year mortality among aging adults.* Scientific Reports, 2020. **10**(1): p. 15760. https://doi.org/10.1038/s41598-020-72045-z

90. Lu, C.Y., et al., *Charlson and Rx-Risk comorbidity indices were predictive of mortality in the Australian health care setting.* Journal of clinical epidemiology, 2011. **64**(2): p. 223-228. https://doi.org/10.1016/j.jclinepi.2010.02.015

91. Nielsen, S., et al., *Benzodiazepine use among chronic pain patients prescribed opioids: associations with pain, physical and mental health, and health service utilization.* Pain medicine, 2015. **16**(2): p. 356-366. https://doi.org/10.1111/pme.12594

92. Lix, L., et al., *Features of physician services databases in Canada.* Chronic Diseases and Injuries in Canada, 2012. **32**(4).

93. Bellows, B.K., et al., *Real-world evidence in pain research: a review of data sources.* Journal of Pain & Palliative Care Pharmacotherapy, 2014. **28**(3): p. 294-304. https://doi.org/10.3109/15360288.2014.941131

94. Bérard, A. and A. Lacasse, *Validity of perinatal pharmacoepidemiologic studies using data from the RAMQ administrative database.* The Canadian journal of clinical pharmacology= Journal canadien de pharmacologie clinique, 2009. **16**(2): p. e360-9.

Abbreviations

AHFS:	American Hospital Formulary Service
BIC:	Bayesian Information Criterion
CP:	Chronic Pain
GMM:	Growth Mixture Modelling
IQR:	Interquartile Range
MQS:	Medication Quantification Scale
MQS-4.0:	Medication Quantification Scale, version 4.0
SAS:	Statistical Analysis System
SD:	Standard Deviation

Supplementary Appendix 1 - The Medication Quantification Scale 4.0 (MQS-4.0)

UQAT
UNIVERSITÉ DU QUÉBEC
EN ABITIBI-TÉMISCAMINGUE



The Medication Quantification Scale 4.0 (MQS-4.0)
An updated index based on prescribers' perceptions of the risk associated with chronic pain medications

	MEDICATION SUBCLASSES	EXAMPLES OF MEDICATIONS*	RISK SCORES (DETRIMENT WEIGHTS)
1	Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) – Selective cyclooxygenase 2 inhibitors (COX-2)	celecoxib (Celebrex®)	5
2	NSAIDs – Salicylates	acetylsalicylic acid (ASA, Aspirin®)	5
3	Other oral NSAIDs	ibuprofen (Advil®, Motrin®), naproxen (Naprosyn®), diclofenac, ketoprofen, meloxicam, piroxicam	6
4	NSAIDs – Topical agents	diclofenac sodium (Pennsaid®), diclofenac diethylamine (Voltaren Emulgel®)	2
5	Various topical agents	various magistral preparations, ketamine cream, benzocaine, lidocaine (Emla®), capsaicin (Zostrix®), Antiphlogistine®, Myoflex®, Tiger Baulm®	2
6	Acetaminophen	Tylenol®	2
7	Acetaminophen in combination with an opioid	acetaminophen with codeine (Triatec-30®, Emprac-et®), with tramadol (Tramacet®) or with oxycodone (Percocet®)	6
8	Short-acting opioids	codeine, fentanyl, hydromorphone, morphine, oxycodone	8
9	Long-acting opioids	methadone, extended release formulations (Codeine Contin® OxyContin®, Hydromorph Contin®, Jurnista®, MS Contin®, Duragesic®)	8
10	Opioids associated with norepinephrine reuptake inhibition	tramadol, tapentadol	6
11	Partial opioid receptor agonists	buprenorphine (Butrans®), butorphanol	6
12	Opioids in combination with an opioid receptor antagonist	buprenorphine/naloxone (Suboxone®), oxycodone/naloxone (Targin®)	6
13	Anticonvulsants – Calcium channel blockers (gabapentinoids)	pregabalin (Lyrica®), gabapentin (Gabapentin®)	5
14	Anticonvulsants – Sodium channel blockers	oxycarbazepine, lamotrigine (Lamictal®)	6
15	Anticonvulsants – Other	levetiracetam (Keppra®), topiramate (Topamax®)	6
16	Antidepressants – Serotonin norepinephrine reuptake inhibitors (SNRIs)	duloxetine (Cymbalta®), venlafaxine (Effexor XR®)	4
17	Antidepressants – Selective serotonin reuptake inhibitors (SSRIs)	citalopram (Celexa®), escitalopram, fluvoxamine (Luvox®), fluoxetine (Prozac®), paroxetine (Paxil®), sertraline (Zoloft®)	4
18	Antidepressants – Serotonin reuptake inhibitors and 5-HT2 receptor antagonists	trazodone	4

	MEDICATION SUBCLASSES	EXAMPLES OF MEDICATIONS*	RISK SCORES (DETRIMENT WEIGHTS)
19	Antidepressants – Specific noradrenergic and serotonergic	mirtazapine (Remeron®)	4
20	Antidepressants – Tricyclic	amitriptyline (Elavil®), nortriptyline (Aventyl®), desipramine	5
21	Antidepressants – Miscellaneous	bupropion (Wellbutrin®)	4
22	Antipsychotics	aripiprazole, chlorpromazine, clozapine, haloperidol, olanzapine (Zyprexa®), quetiapine (Seroquel®)	6
23	Barbiturates	phenobarbital, primidone	8
24	Benzodiazepines	lobazam, clonazepam (Rivotril®), alprazolam (Xanax®), bromazepam, chlordiazepoxide, diazepam (Valium®), flurazepam, lorazepam (Ativan®), midazolam, oxazepam	8
25	Various anxiolytics, sedatives, and hypnotics	buspirone, hydroxyzine (Atarax®), promethazine, zopiclone, zolpidem tartrate	6
26	Centrally acting skeletal muscle relaxants	cyclobenzaprine (Flexeril®), methocarbamol (Robax®)	5
27	GABA-Derivative skeletal muscle relaxants	baclofen (Lioresal®)	5
28	Miscellaneous muscle relaxants	orphenadrine (Norflex®)	4
29	Synthetic cannabinoid (under prescription)	nabilone (Cesamet®)	6
30	Medical/therapeutic cannabis	vaporized, vaped, oral, oromucosal, topical	6
31	Antimigraine agents – 5HT-1 receptor agonists (triptans)	sumatriptan (Imitrex®)	4
32	Antimigraine agents – Calcitonin gene-related peptide (CGRP) antagonists	erenumab (Aimovig®)	4
33	Antimigraine agents – Miscellaneous	pizotifen (Sandomigran®)	5
34	Corticosteroids – Oral	prednisone, prednisolone	7

* According to medications approved and available in Canada at the time of the study.

STEPS FOR CALCULATING THE MQS-4.0 SCORE, A MEASURE OF THE RISK ASSOCIATED WITH THE USE OF MEDICATIONS FOR THE TREATMENT OF CHRONIC PAIN:



1. Conduct an assessment of all prescribed and over-the-counter medications used by the participant, including medical cannabis use.
2. Assign scores based on the different medication subclasses listed in the above table.
3. Sum these scores to obtain a total score.
4. Utilize this new continuous variable as an outcome, a determinant, a confounder, or an effect modifier in your clinical or epidemiologic research projects.

TO CITE OR FOR MORE INFORMATION:

De Clifford-Faugère G, Nguena Nguefack HL, Godbout-Parent M, Diallo MA, Guénette L, Pagé MG, Choinière M, Harden RN, Beaudoin S, Boulanger A, Pinard AM, Lussier D, De Grandpré P, Deslauriers S, Lacasse A. (2023) The Medication Quantification Scale 4.0: An updated index based on prescribers' perceptions of the risk associated with chronic pain medications. *The Journal of Pain*. doi:10.1016/j.jpain.2023.09.010

URL: https://pubmed.ncbi.nlm.nih.gov/37838346/

Correspondence: Anais.Lacasse@uqat.ca

```
/* SAS code for the calculation of MQS-4.0 total score for each patient
before or after an index date using medication claim data.

    Year: 2023
    Author: Hermine L. Nguena N.


PDIP_Data_MQS: dataset that will be used for calculating the MQS-4.0
total score. This dataset contains information on prescription claims
and the index date.

surv_data: dataset containing survey data or other type of data,
including an index date (e.g., date of survey completion)

pharma_serv: Dataset containing all pharmaceutical information of each
patient (several lines per patient, each line corresponding to one
medication claim)

Variables

NOINDIV: patient ID
INDEX_DATE: index date
DATESERVICE: Date of claim
CLASSE_AHFS: AHFS (American Hospital Formulary Service) class of the
claimed medication
SMED_COD_DENOM_COMNE: Common Drug Name Code for the Medication
SMED_COD_FORME_MED: Code indicating the pharmaceutical form of the
medication
SMED_COD_DIN: Code corresponding to the Drug Identification Number
(DIN)

All M4_... variables, containing risk scores for each medication
subclass, are created using risk scores indicated in the Table 2 of the
article. */


data cohort.PDIP_Data_MQS;
merge cohort.surv_data (in=a keep=NOINDIV INDEX_DATE)
cohort.pharma_serv (in=b keep=NOINDIV DATESERVICE CLASSE_AHFS
SMED_COD_DENOM_COMNE SMED_COD_FORME_MED SMED_COD_DIN);
by NOINDIV_SRAP;
if a and DATESERVICE ge (INDEX_DATE-28) and DATESERVICE le INDEX_DATE;
/* 28 can be remplaced by the number of days before index date and -
can be remplaced by + if MQS-4.0 is calculated after index date*/
If classe_AHFS = '280804' AND SMED_cod_denom_comne in (47327,47346)
THEN M4_COX2= 5;/* NSAIDs—COX-2*/
Else M4_COX2 = 0;
If classe_AHFS = '280804' AND SMED_cod_denom_comne in (00143) THEN
M4_SALI = 5; /*NSAIDs—salicylates*/
Else M4_SALI = 0;
If classe_AHFS = '280804' AND SMED_cod_denom_comne NOT in
(47327,47346,00143) THEN M4_NSAID = 6; /*Other oral NSAIDs*/
Else M4_NSAID = 0;
If substr(CLASSE_AHFS,1,4)='8406' AND SMED_cod_denom_comne IN
(39042,00780,37768,46585,02548,38405,45448,47299,47884,09724,09737,0935
0,10881,17758,33413,38119,39055,04550,04563,04589,46390,46420,47598,087
62,47768) THEN M4_AINS_TOPIC= 2; /*NSAIDs—Topical agents*/
```

```
Else M4_AINS_TOPIC= 0;
If substr(CLASSE_AHFS,1,4)='8406' AND SMED_cod_denom_comne = 45489 THEN
M4_TOPIC= 2; /* Various topical agents: Capsaicine*/
Else if SMED_cod_denom_comne  IN (40797 , 43345 , 43358 , 43930 , 46008
, 46050 , 46433 , 46481 , 46703 , 47750 , 05265 , 05278 , 05291 ,
18205) THEN M4_TOPIC= 2; /* Various topical agents: Lidocaine*/
Else M4_TOPIC=0;
If classe_AHFS = '280892' AND SMED_cod_denom_comne = 00039 THEN
M4_ACET= 2; /*Acetaminophen*/
Else M4_ACET= 0;
If substr(CLASSE_AHFS,1,4)='2808' AND SMED_cod_denom_comne IN
(47567,38496,46037,46168) THEN M4_ACET_OP= 6;/* Acetaminophen in
combination with an opioid*/
Else M4_ACET_OP= 0;
If classe_AHFS ='280808' AND SMED_COD_FORME_MED IN
(01827,02001,02262,02552,00203) THEN M4_OP_C= 8; /* Short-acting opioids
*/
Else M4_OP_C= 0;
If classe_AHFS = '280808' AND SMED_COD_FORME_MED IN
(00145,00435,05133,05162,05569,05570,05580,05592,05596,05597,05598,0560
0,05602,05603,05604,05611,05621,05622,05623,05624,05625,05643,05677,056
85) THEN M4_OP_L= 8; /* Long-acting opioids*/
Else M4_OP_L= 0;
If classe_AHFS = '280808' AND SMED_cod_denom_comne IN (47654,47860)
THEN M4_OP_IRN= 6; /* Opioids associated with a norepinephrine reuptake
inhibitor */
Else M4_OP_IRN= 0;
If classe_AHFS = '280812' AND SMED_cod_denom_comne IN (38847,44528)
THEN M4_ANTA_OPIAC= 6; /* Partial opioid receptor agonizts*/
Else If classe_AHFS = '990003' AND SMED_cod_denom_comne = 47835 THEN
M4_ANTA_OPIAC= 6;
Else M4_ANTA_OPIAC= 0;
If substr(CLASSE_AHFS,1,4)='2810' AND SMED_cod_denom_comne IN
(47725,47846) THEN M4_OP_ANTA_OPIAC= 6; /* Opioids in combination with
an opioid receptor antagonist*/
Else M4_OP_ANTA_OPIAC= 0;
If classe_AHFS = '281292' AND SMED_cod_denom_comne IN
(47080,47100,47229,47463,47571,38951,39393,44073) THEN M4_ANTICON_gaba=
5; /* Anticonvulsants—Calcium channel blockers (gabapentinoids)*/
Else M4_ANTICON_gaba=0;
If classe_AHFS = '281292' AND SMED_cod_denom_comne IN
(01404,47110,47430,47847,47875,47957) THEN M4_ANTICON_sodium= 6; /*
Anticonvulsants—Sodium channel blockers*/
Else M4_ANTICON_sodium=0;
If classe_AHFS = '2812 92' AND SMED_cod_denom_comne NOT IN
(47080,47100,47229,47463,47571,38951,39393,44073,01404,47110,47430,4784
7,47875,47957) THEN M4_ANTICON_other= 6; /* Anticonvulsants—Other*/
Else M4_ANTICON_other= 0;
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN (47118,47714)
THEN M4_ANTIDEP_IRSN= 4; /* Antidepressants—SNRIs*/
Else M4_ANTIDEP_IRSN=0;
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN
(45504,45630,45633,47061,47317,47553) THEN M4_ANTIDEP_ISRS= 4; /*
Antidepressants—SSRIs*/
Else M4_ANTIDEP_ISRS=0;
```

```
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN (43137,47093)
THEN M4_ANTIDEP_5_HT2= 4; /* Antidepressants—SSRIs and 5-HT2 receptor
antagonists */
Else M4_ANTIDEP_5_HT2=0;
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN (47408) THEN
M4_ANTIDEP_NetS= 4; /* Antidepressants—Specific noradrenergic and
serotonergic */
Else M4_ANTIDEP_NetS=0;
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN
(00429,00442,02522,03198,04784,06578,08294,09906,14781,37443) THEN
M4_ANTIDEP_tri = 5; /* Antidepressants—Tricyclics*/
Else M4_ANTIDEP_tri=0;
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN
(07280,09698,42058,47005,47285) THEN M4_ANTIDEP_other= 4; /*
Antidepressants—Miscellaneous*/
Else M4_ANTIDEP_other=0;
If classe_AHFS = '281608' THEN M4_ANTIPSY= 6; /* Antipsychotics*/
Else M4_ANTIPSY= 0;
If classe_AHFS  IN ('281204','282404') THEN M4_BARB= 8; /* Barbiturates
*/
Else M4_BARB= 0;
If classe_AHFS IN ('282408','281208') THEN M4_BENZO= 8; /*
Benzodiazepines*/
Else M4_BENZO= 0;
If classe_AHFS = '282492' AND SMED_cod_denom_comne IN
(01703,43047,47912,04706,06045,08177,42058,45609) THEN M4_ANXIO_SEDAT=
6; /* Various anxiolytics, sedatives, and hypnotics */
Else M4_ANXIO_SEDAT= 0;
If classe_AHFS= '122004' THEN M4_MYO_central= 5; /* Centrally acting
skeletal muscle relaxants */
Else M4_MYO_central = 0;
If classe_AHFS= '122012' THEN M4_MYO_gaba= 5; /* GABA (gama-aminobutyric
acid)-derivative skeletal muscle relaxants */
Else M4_MYO_gaba= 0;
If classe_AHFS IN ('122008','122092') THEN M4_MYO_divers= 4; /*
Miscellaneous muscle relaxants */
Else M4_MYO_divers= 0;
If SMED_cod_denom_comne = 42838  THEN M4_CANNABINOIDS= 6; /* Synthetic
cannabinoids (under prescription)*/
Else M4_CANNABINOIDS= 0;
If classe_AHFS = '283228' THEN M4_ANTIMIGRAINE_5HT1= 4; /* Antimigraine
agents—5HT-1 receptor agonizts (triptans) */
Else M4_ANTIMIGRAINE_5HT1= 0;
If classe_AHFS= '283292' AND SMED_COD_DIN  IN (02497859,02509474) THEN
M4_ANTIMIGRAINE_CGRP= 4; /* Antimigraine agents—CGRP antagonists */
Else M4_ANTIMIGRAINE_CGRP= 0;
If classe_AHFS = '283292' AND SMED_COD_DIN  NOT IN (02497859,02509474)
THEN M4_ANTIMIGRAINE_divers= 5; /* Antimigraine agents—Miscellaneous */
Else M4_ANTIMIGRAINE_divers= 0;
If substr(CLASSE_AHFS,1,4)= '6804' AND SMED_cod_denom_comne IN
(02197,02587,03952,46420,06175,07956) THEN M4_CORTICO_O= 7; /*
Corticosteroids—Oral */
Else M4_CORTICO_O= 0;
If classe_AHFS = '240816'   AND SMED_cod_denom_comne = 10751 THEN
M4_CLON= 5; /*Clonidine*/
Else M4_CLON= 0;
```

```
If classe_AHFS = '240404' AND SMED_cod_denom_comne = 44970 THEN M4_MEX=
6; /*Mexiletine*/
Else M4_MEX=0;
run;

*Intermediate MQS-4.0 score for each line (several line per patient);
data cohort.PDIP_Data_MQS;
set cohort.PDIP_Data_MQS;
MQS_4.0_int=
M4_COX2+M4_SALI+M4_NSAID+M4_AINS_TOPIC+M4_TOPIC+M4_ACET+M4_ACET_OP+M4_O
P_C+M4_OP_L+M4_OP_IRN
+M4_ANTA_OPIAC+M4_OP_ANTA_OPIAC+M4_ANTICON_gaba+M4_ANTICON_sodium+M4_AN
TICON_other+M4_ANTIDEP_IRSN+M4_ANTIDEP_ISRS
+M4_ANTIDEP_5_HT2+M4_ANTIDEP_NetS+M4_ANTIDEP_tri+M4_ANTIDEP_other+M4_AN
TIPSY+M4_BARB+M4_BENZO+M4_ANXIO_SEDAT+M4_MYO_central
+M4_MYO_gaba+M4_MYO_divers+M4_CANNABINOIDS+M4_ANTIMIGRAINE_5HT1+M4_ANTI
MIGRAINE_CGRP+M4_ANTIMIGRAINE_divers+M4_CORTICO_O+M4_CLON+M4_MEX;
run;

/* If the same medication (SMED_cod_denom_comne) is claimed more than
once within the study period for a patient, then consider it only once
*/
proc sort data=cohort.PDIP_Data_MQS;
by NOINDIVSMED_cod_denom_comne;
run;

data cohort.PDIP_Data_MQS;
set cohort.PDIP_Data_MQS;
by NOINDIV SMED_cod_denom_comne;
if first.SMED_cod_denom_comne;
run;

proc sort data=cohort.PDIP_Data_MQS;
by NOINDIV_SRAP;
run;

/*MQS-4.0 total score for each participant (one line per patient)*/

data cohort.PDIP_Data_MQS; set cohort.PDIP_Data_MQS;
 retain MQS_4.0;
  by NOINDIV_SRAP;
  if first.NOINDIV then do;
    MQS_4.0=0;
  end;
MQS_4.0+ MQS_4.0_int;
if last.NOINDIV_SRAP;
run;


/*To check MQS-4.0 distribution*/
proc means data=cohort.PDIP_Data_MQS N mean std Q1 median Q3 min max;
var MQS_4.0;
run;

** For patients covered by public drug insurance plan, but with no
claims during the study period, consider MQS-4.0 = 0 ***;
```

Supplementary Appendix 2 - Growth Mixture Modelling

Model fit indices tables

Table legend:
[1] 1 = linear (straight line); 2 = linear + quadratic (u-shaped curve/parabola) components; 3 = linear + quadratic + cubic components [2] BIC: Bayesian information criterion NA: not applicable
* One or more groups in the model had less than 5% of participants
** Entropy < 0.8
*** Lowest proportion of individuals per group with posterior probability group ≥ 0.8 **Bold text:** Model which best fits the data and respected all criteria (lowest BIC absolute value among trajectory groups that respected the 5% criteria as well as entropy ≥ 0.8 and highest proportion of individuals per group with posterior probability group ≥ 0.8)

Model fit indices for MQS-4.0 risk score trajectories in the whole study sample

Number of trajectories	Trajectory shape 1	Entropy	BIC 2 (n=8,760)
1	1	NA	1171065.0
1	2	NA	1158975.0
1	3	NA	1158981.0
2	1	0.9416529	1162049.0
2**	2	0.6905794	1151421.0
2**	3	0.6905768	1151436.0
3	1	0.9316713	1156299.0
3**	2	0.7687867	1148024.0
3**	3	0.7687912	1148049.0
4	**1**	**0.8583271**	**1150711.0**
4***	2	0.8266736	1143696.0
4***	3	0.8552526	1143785.0
5**	1	0.7892655	1149201.0
5*	2	0.7926603	1141657.0
5*	3	0.8470322	1142057.0
6*	1	0.8019192	1147982.0
6*	2	0.7529791	1141961.0
6*	3	0.7914570	1141514.0

Model fit indices for trajectories of the number of analgesics and co-prescribed medications in the whole study sample

Number of trajectories	Trajectory shape 1	Entropy	BIC 2 (n=8,760)
1	1	NA	19946502.1
1	2	NA	19946502.1
1	3	NA	19946502.1
2	1	0.9568665	615718.8
2	2	0.9568659	615731.0
2	3	0.9668690	615742.6
3	1	0.9861390	489198.1
3	2	0.9861651	489206.9
3	3	0.9861782	489228.7
4	1	0.9694729	457213.2
4	2	0.9694953	457172.0
4	3	0.9694593	457206.6
5	1	0.9532880	444880.0
5	**2**	**0.9535563**	**444799.4**
5	3	0.9534806	444846.1
6*	1	0.9402202	441117.6
6*	2	0.9403927	441041.7
6*	3	0.9534806	441100.5