Trends in benzodiazepine and alternative hypnotic use in relation with multimorbidity among older adults in Quebec, Canada

Trends in benzodiazepine and alternative hypnotic use in relation with multimorbidity among older adults in Quebec, Canada

Authors:

Emmanuelle Gosselin B.Pharm, MSc.[1,2,4] (ORCID ID: **:** 0000-0003-2824-8633)

Marc Simard M.Sc.[1,2]

Carlotta Lunghi, Ph.D.[3]

Caroline Sirois B.Pharm., Ph.D.[1,2,4]

[1]Laval University, Quebec, Canada

[2]Institut national de santé publique du Québec, Québec, Canada

[3]Université du Québec à Rimouski, Lévis, Québec, Canada

[4]Centre d'excellence sur le vieillissement de Québec, Québec, Canada

Corresponding author: Emmanuelle Gosselin (emmanuelle.gosselin.1@ulaval.ca)

ORCID ID (Emmanuelle Gosselin): 0000-0003-2824-8633

DECLARATION

Funding

Emmanuelle Gosselin received a scholarship from the Centre d'excellence en vieillissement de Québec (CEVQ) and the Institut sur le vieillissement et la participation sociale des aînés (IVPSA). Caroline Sirois is the recipient of a Junior 1 research award from the Fonds de recherche du Québec — Santé (FRQS) and of a grant from the Centre de recherche sur les soins et les services de première ligne de l'Université Laval.

Conflict of interest

The authors have no conflict of interest to declare.

Availability of data and material

The authors do not have permission to share the data extracted for this study from the Quebec Integrated Chronic Disease Surveillance System database.

Code availability

Not applicable

Author's contribution

Emmanuelle Gosselin conceptualized the study, performed the analysis, interpreted the data and wrote the initial draft of the manuscript. Caroline Sirois conceptualized the study, contributed to the analyses, interpreted the data, reviewed and revised the present manuscript. Marc Simard conceptualized the study, performed the analysis, interpreted the data and revised the manuscript. Carlotta Lunghi interpreted the data and critically revised the manuscript. All authors gave final approval of the manuscript.

Acknowledgment

The authors thank all members of the Quebec Integrated Chronic Diseases Surveillance System team for their valuable assistance during the research.

Abstract:

Background Benzodiazepines and other hypnotic alternatives are associated with increased risks of adverse events. Heightened awareness of risks may have changed prescribing habits over the years. However, these trends are not fully described, especially in vulnerable people such as multimorbid older adults.

Objective We aimed to describe the annual prevalence of benzodiazepine and other hypnotic use in relation to multimorbidity among older adults in the province of Quebec, Canada, from 2000 to 2016.

Method We conducted a population-based study using the Quebec Integrated Chronic Disease Surveillance System. We included all individuals aged ≥ 66 years covered by the public drug plan. For each year, we evaluated the sex- and age-standardized proportion of benzodiazepine and other hypnotic users, defined as individuals with at least one drug claim in the year. We stratified our results according to multimorbidity and used log-binomial regression to study trends.

Results The proportion of individuals using benzodiazepines decreased from 34.8% in 2000 to 24.8% in 2016 (p for trend < 0.001). Multimorbid people (≥ two chronic diseases) remained the highest users over the years, with 43.3% and 30.6% of them being users in 2000 and 2016, respectively. Conversely, the proportion of users increased for other hypnotics, particularly for trazodone and quetiapine, rising from 5.4% to 8.4% (p<0.001), and especially among multimorbid individuals (from 7.4% to 11.6%).

Conclusion Older adults used benzodiazepines less frequently but quetiapine and trazodone more frequently in recent years. The use of these medications, particularly in multimorbid people at risk of adverse events, must be addressed.

Key points:

- Benzodiazepines are widely used and are associated with an important risk of adverse effects.
- Alternative medications given as hypnotics are not considered safer. It is important to determine the extent to which the most vulnerable groups, such as multimorbid people, are exposed to these medications.
- Despite a significant decrease in the proportion of benzodiazepine users in recent years, the prevalence remains high in older adults, notably in multimorbid individuals.
- Multimorbid individuals are also more prone to receive alternative medications used as hypnotics.
- Considering the iatrogenic risk entailed, it seems paramount to extend access to reimbursements for non-pharmacological alternatives.

Keywords : Benzodazepines, Hypnotics, Potentially Inappropriate Medications, Multimorbidity

1. Background

The aging of the population is accompanied by a significant increase in the prevalence of chronic diseases [1,2]. Consequently, multimorbidity, which is usually defined as the co-occurrence of two or more chronic diseases, is frequent [1,2]. Treating multimorbidity often entails a significant number of prescribed medications [3,4]. However, taking a large number of medications is associated with a higher probability of receiving potentially inappropriate medications (PIMs), whose risks may be greater than their benefits [5]. Almost half of adults older than 65 are exposed to at least one PIM in a given year [6,7]. In the province of Quebec, Canada, benzodiazepines are the most frequent class of PIMs [6]. Considering their associated risk of falls, hip fractures, hospitalizations and cognitive dysfunction [8-12], it is important to determine the extent to which the most vulnerable groups, such as multimorbid people, are exposed to benzodiazepines. Few studies have focused on the use of hypnotics and multimorbidity, although some of them indicated that sicker people were more likely to receive these medications [13,14]. Moreover, there are no recent population-based data that explore trends in benzodiazepine use over time in multimorbid older adults.

In recent years, awareness and concerns about benzodiazepine-related harm have risen among health professionals [15,16]. This could have contributed to the consideration of alternative medications for insomnia. Such medications include notably low-dose antidepressants and antipsychotics [17-19]. However, most of these medications have shown very little or no benefit and have generated serious concerns because of potential adverse effects [18,20]. Most of these medications are thus considered as potentially inappropriate by experts [21,22]. Nevertheless, it is unknown to what extent older adults with multimorbidity are now using these medications.

Our study aimed to describe trends in the prevalence of benzodiazepine users among older adults in Quebec between 2000 and 2016, and to stratify the trends according to the number of chronic diseases presented by the individuals. Additionally, we sought to assess whether the proportion of users of other potentially inappropriate hypnotic medications has changed over the years by studying trends in their use over the same period as benzodiazepines and stratifying use according to the individuals' number of chronic diseases.

2. Methods

2.1 Design and setting

We conducted a population-based study using the Quebec Integrated Chronic Disease Surveillance System (QICDSS), developed by the Institut national de santé publique du Québec (INSPQ). The QICDSS is composed of five health administrative databases, including the health insurance registry, the vital statistics death database, the physician claim database, the hospital discharge database, and the pharmaceutical service database. The physician claim database includes diagnosis codes from the International Classification of Diseases 9th edition (ICD-9), and the hospital discharge database includes all diagnosis codes using ICD-10-CA. Because of the public universal medical coverage, the physician and hospital databases include information on all individuals in the province of Quebec. The pharmaceutical service database includes all claims for prescribed medications reimbursed by the Quebec public drug plan, which covers around 90% of the population 65 and older. The database includes medications dispensed in community pharmacies but does not capture medications administered in hospitals. It has been shown to provide accurate and valid information [23, 24]. Data were extracted from the QICDSS for each fiscal year from 2000 to 2016, with a fiscal year running from April 1st to March 31st of the following year.

2.2 Study population

All individuals aged 66 and over insured by the Quebec public drug plan were included in the study. Seniors living in long-term care facilities were excluded since the data on their medication use does not appear in the QICDSS (see Appendix 1). For each year, we included all the individuals that were covered by the public drug plan for the whole year except those who died or were transferred to long-term care. In these latter cases, individuals were included for the specific year of the event until their death or transfer.

2.3 Medication exposure

We included all benzodiazepines listed on the Quebec public drug plan list since 2000, without regard to the indication of treatment, dosage, or whether they were short- or long-acting (see Appendix 2 for complete list). We excluded midazolam as it is only available in an injection form and is most often used for indications other than insomnia or anxiety. Furthermore, we identified all the alternative PIMs listed in the 2019 Beers criteria [21] that can be used ~~as~~ off-label ~~substitutes to benzodiazepines~~ for their hypnotic effects, in addition to trazodone (Appendix 2). While not considered as inappropriate by Beers criteria, recent guidelines of the

American Academy of Sleep Medicine do not recommend trazodone use given the very little evidence of effectiveness [20]. Again, we did not distinguish between the indication of treatment or dosage prescribed, except for quetiapine, for which we extracted data on the 25mg tablets only, a dosage that is more likely to be used for the hypnotic effects [18]. We did not include medications that are appropriate alternatives to benzodiazepines, such as selective serotonin reuptake inhibitors (SSRIs) for anxiety. All studied drugs were extracted from the pharmaceutical service database using the common name code, which is a unique code per pharmacological substance and corresponds to the 5th ATC level.

Medication was assessed yearly and a person was considered exposed to a medication if there was a least one claim in a given fiscal year for a study medication, regardless of the days' supply, length of treatment, or number of renewals. A person had to qualify each year to be considered a "user" of a specific medication in a given year. Individuals could contribute to both groups of medications (benzodiazepines and other PIMs) for the same year.

2.4 Multimorbidity assessment

Cumulative chronic disease count was obtained by summing diseases. Chronic diseases were identified using the validated Combined Comorbidity Index list of 31 conditions [25] (Appendix 3). A look-back window of five years was used to single out the chronic diseases from the QICDSS files. To identify the conditions, we used validated case definitions (one diagnosis code during hospitalization or two outpatient diagnostic codes, with at least 30 days apart within the 5 years look-back) [26]. We captured the cases from the hospitalization and physician claim databases. Those databases provide complete data for the entire population since more than 98% of individuals in the province are covered continuously by the public health insurance plan. Multimorbidity was defined as the presence of two or more chronic diseases.

2.5 Statistical analysis

We calculated the proportion of users of each medication category, and the proportion of users of specific medications within categories, for each year between 2000 and 2016. We used as a denominator the number of individuals 66 years old and over covered by the public drug plan within a year. We used log-binomial regression to assess age- and sex-standardized trends in the prevalence of benzodiazepine use, using the 2011

Quebec population as a reference [27]. Trends in the use of benzodiazepines and alternative PIMs were further stratified according to the number of chronic diseases, which were categorized as follows: 0, 1, 2, 3 to 5, and 6 and more diseases.

We performed two sensitivity analyses. First, we limited inclusion to patients with continuous enrollment throughout the year (i.e., who did not die and were not transferred to long-term care) to evaluate the potential impact on the estimates. Second, we used the Combined Comorbidity Index, instead of the number of chronic conditions, to stratify trends [25]. The Combined Comorbidity Index attributes weight to each chronic disease and better reflects the weight of each disease in order to predict mortality [25].

The statistical significance was set at 0.01. All analyses were performed using SAS Enterprise 9.4 software (SAS Institute, Cary, NC).

2.6 Ethics approval

QICDSS data is housed in a secure server at the INSPQ. Its use has been approved by the Quebec Access to Information Commission for surveillance purposes. Data is completely and irrevocably de-identified and does not allow individual reidentification.

3. Results

The total population over the study period went from 779,667 individuals in 2000 to 1,202,705 individuals in 2016. There was a greater number of women each year and mean age (around 76 years) slightly increased over time (Table 1). The mean number of chronic diseases increased from 1.97 to 2.08 in the 17 years.

3.1 Benzodiazepine trends and multimorbidity

The adjusted proportion of individuals aged 66 and older that received at least one benzodiazepine decreased each year, from 34.8% [99% CI = 34.6-35.0] in 2000 to 24.8% [24.7-24.9] in 2016 (decrease in relative prevalence: -1.9% per year, p-value for trend < 0.0001). This represents an absolute decrease of about 10% in the proportion of users over the 17 years. This decline in the proportion of users was observed for all benzodiazepines except for clonazepam where the proportion increased slightly from 3.2% [3.2-3.3] to 4.2% [4.1-4.2] (Figure 1). Lorazepam was the most prescribed benzodiazepine every year, with 15.3% [15.1-15.4]

of users in 2000 and 11.2% [11.2-11.3] in 2016, followed by oxazepam (9.7% [9.6-9.8] to 6.4% [6.3-6.4]) (Figure 1). The prevalence of benzodiazepine users was persistently higher in women than in men (Figure 1), but the gap between sexes appeared to narrow over time. In 2000, 40.6% [40.3-40.8] of women claimed at least one prescription, compared to 27.4% [27.1-27.6] of men. The proportions decreased in 2016 to 29.5% [29.3-29.7] for women and 18.5% [18.4-18.7] for men, respectively.

People with multimorbidity were at consistently higher risk of using a benzodiazepine each year (Figure 2a). In 2000, 43.3% [43.0-43.6] of multimorbid older adults received at least one benzodiazepine while the corresponding proportion was 27.1% [26.8-27.3] among individuals without multimorbidity. Both proportions decreased in the 17 years studied, with 30.6% [30.4-30.8] and 20.2% [20.1-20.4] of individuals with and without multimorbidity using benzodiazepines in 2016, respectively. Likewise, benzodiazepine use was more common as the number of chronic diseases increased. In 2000, 54.9% [53.9-55.8] of older individuals with six and more chronic diseases had at least one benzodiazepine claim, compared to 21.5% [21.2-21.8] of older individuals with no chronic diseases. The respective proportions were 39.6% [39.1-40.2] and 17.9% [17.6-18.1] in 2016. Those with six and more chronic diseases have nonetheless experienced the greatest absolute drop in use over the period: 15.3% (from 54.9% to 39.6%), while the same proportion declined by 3.7% (from 21.5% to 17.8%) among individuals without chronic disease.

3.2 Alternative PIM trends and multimorbidity

~~Parallel to the decline in benzodiazepine use,~~ Alternative PIM use increased from 5.4% [99% CI: 5.3-5.5] in 2000 to 8.4% [8.3-8.5] in 2016 (Figure 3).The proportion of quetiapine users went from less than 0.1% [0.06-0.08] to 2.2% [2.2-2.3], while the proportion of trazodone users increased from 1.2% [1.1-1.2] to 3.3% [3.3-3.4]. Overall, the risk of receiving an alternative PIM of any type increased by 1.03% each year (p for trend <0.0001). Women were greater users of alternative PIMs than men. For example, the proportion of users were 10.2% and 6.1% in 2016, respectively. However, the proportion of users of all types of studied medications combined (both benzodiazepines and/or alternative PIMs) decreased over the 17-year study period, from 36.7% [36.6-36.9] to 29.4% [29.2-29.5] (Figure 4). On the absolute scale, the proportion of users who were dispensed only benzodiazepines decreased by 10.4% while the proportion of users who used

only alternative PIM increased by 2.7%. The proportion of older individuals who used both types of medications has remained relatively stable, from 3.4% in 2000 to 3.8% in 2016.

Individuals with multimorbidity were at higher risk of using at least one alternative PIM. In 2016, 11.6% [11.4-11.7] of individuals with multimorbidity were users of alternative PIMs, whereas 5.9% [5.8-6.0] of individuals with no multimorbidity were using them. Individuals with six chronic diseases and more experienced the largest absolute increase in use between 2000 and 2016 (7.9%, from 10.7 % to 18.6%) compared to those without chronic diseases (2.3%, from 2.7% to 5.0%) (Figure 2b).

The results of the sensitivity analysis showed that the exclusion of patients who died or were transferred to long-term care had little impact on the conclusions obtained (Appendix 4). The annual prevalence of benzodiazepine use in this population with continuous enrollment decreased by approximately 0.4% compared to the whole population. The trends were therefore not impacted and the conclusions are consistent with the main analysis. Similarly, the sensitivity analyses using the Combined Comorbidity Index instead of the number of chronic diseases yielded similar results to the main analysis, with people having a greater burden of disease being the largest users of the studied medications (Appendix 5).

4. Discussion

From 2000 to 2016, the prevalence of benzodiazepine use decreased from 34.8% to 24.8% in the older population in Quebec, reflecting substantial changes in prescription behavior over the period. In contrast, PIMs often used as alternatives to benzodiazepines were dispensed to a higher proportion of older people, from 5.4 % to 8.4%. Multimorbid individuals, and especially those with a larger number of chronic diseases, remained more likely to use benzodiazepines and other alternative PIMs.

Other studies have shown similar downward trends in benzodiazepine use [28-32]. Recent guidelines and awareness campaigns surrounding these drugs, such as the Choosing Wisely campaign, may notably have driven these reductions [15, 21]. In Ontario, a neighboring province of Quebec, the prevalence of use fell from 23.2% in 1998 to 14.8% in 2013, with a reduction of 36.1% of the total initial users [33]. The decrease was accentuated in 2011, following the adoption of a law regulating the prescription of controlled substances

such as benzodiazepines to ensure their optimal use [33]. In our study, the prevalence of use decreased for each type of benzodiazepine, except for clonazepam. This phenomenon is consistent with what has been observed in other studies [29,32,34], and may be explained by the apparent clinical superiority of this molecule for the treatment of conditions such as anxiety disorder [35,36].

Of all the alternative PIMs selected, only trazodone and quetiapine showed a progressive increase in the proportion of users over time. Nonetheless, the total use of alternative PIMs increased from 5.4% to 8.4%. In Ontario, Iaboni and al. previously documented a similar pattern for these two medications from 2002 to 2013 [16]. Multimorbid individuals were the largest users of benzodiazepines and alternative PIMs. They might also be more likely to be dual users of both PIMs and benzodiazepines. Those findings are consistent with previous studies conducted on multimorbidity and hypnotic use. In Iceland, a study revealed that among individuals of all ages who were prescribed hypnotic medications, 85% were considered multimorbid, making multimorbidity a significant risk factor for the use of hypnotic medications (OR=14.9; 95%CI 14.4-15.4) [14]. In addition, Van Eijk et al. documented a relationship between benzodiazepine use and multimorbidity in their cohort study in the Netherlands; the risk of receiving a benzodiazepine was increased for both older multimorbid men (OR: 1.40; 95% CI:1.36-1.44) and women (1.46;1.40-1.52) [37]. Multimorbid individuals were also more likely to repeat prescriptions [37]. Some hypotheses can be made to explain why multimorbid individuals are more at risk of being prescribed benzodiazepines and other alternative PIMs. On one hand, multimorbidity is closely related to polypharmacy, as the treatment of chronic diseases often requires the use of simultaneous different drugs, and polypharmacy is an important risk factor for being prescribed a PIM [5]. Yet such logic is probably insufficient to explain the relation observed. Among individuals with chronic physical illness, the prevalence of mental health problems such as depression or anxiety is high [37-40]. Treatment of those patients seems to be different, and it was suggested that depressed people with comorbidities were more likely to be prescribed benzodiazepines than depressed people with no other conditions [37]. This situation might denote the high complexity clinicians face when dealing with both mental and physical health conditions [41]. Benzodiazepine and alternative PIMs use has also been demonstrated to be more prevalent in people with physical illnesses, including chronic pain, pulmonary diseases, osteoporosis [13,37,42]. Given their diseases, those patients are already more at risk of

harm from benzodiazepines and alternative PIMs, such as a hip fracture [13,43]. Furthermore, among people with a larger number of chronic diseases, a greater proportion uses a higher dosage of hypnotic medications [44]. Long-term hypnotic users (both multimorbid and non-multimorbid) also seem to experience a higher risk for mortality, which increases along with dosage [44]. These facts highlight the problematic nature of benzodiazepine and alternative PIM use, particularly among multimorbid people, and support the importance of heightened attention when prescribing benzodiazepine to vulnerable populations. Considering that 30.6% of multimorbid individuals were using benzodiazepines and 11.6% were using other alternative PIMs in 2016 in our study, it appears paramount to address this issue.

Our study has important strengths. It is the first longitudinal study that examines trends of benzodiazepine and other alternative PIM use in relation to multimorbidity in virtually the entire population of older adults in the province of Quebec. We used a population-based database that captures accurate and valid data on medications and diagnoses of chronic diseases. Moreover, we used validated case definitions to assess multimorbidity. Nonetheless, certain limitations should be noted. We did not include z-drugs, which are similar to benzodiazepines, since they are not covered by the public drug plan. However, we expect the impact to be minimal since prescribers often favor medications that are reimbursed under the drug plan, especially for multimorbid patients who already have a considerable number of medications to buy. Similarly, natural products such as melatonin are not taken into account for the same reason. Our results may thus underestimate the use of hypnotics by seniors in Quebec. We have also restricted our analysis to PIMs, but some medications may be suitable alternatives to benzodiazepines, such as SSRIs, to treat anxiety disorders. It is possible that the use of these medications increased during the period, which would correspond to an adequate switch from benzodiazepines. Unfortunately, as it was not possible to identify the indication of these alternatives, the trends in their use could not be explored in the context of this study. We also recognize that while we categorized the included medications as potentially inappropriate, there might be instances where the benefits outweigh the risks. However, since we cannot assess the indication of medications prescribed, it is impossible to determine what condition was treated. Therefore, it is difficult to estimate what proportion of use is clinically justified. Also, people 66 and older with private drug insurance plans are not included in the QICDSSS database. However, they represent a minority of this population (approximately

7.5% each year), but our results may not be generalizable to this group [23]. Furthermore, the pharmaceutical database does not capture medications dispensed during hospitalization. However, our study aimed to assess community use only, so inpatient use would not have been included in the analysis. We did not assess the doses or the duration of treatments. Although the risks associated with the use of benzodiazepines increase with longer use, higher doses, and longer half-life, there are also adverse events associated with short-term use or the initiation of therapy, such as falls [45,46]. Consequently, we thought that even a single dispensation in an individual would be relevant to draw up a population portrait of benzodiazepine use. Future research should address those aspects to better define the associated risks. Finally, as this study capture medication claims, some individuals considered exposed to the medication might not be exposed if they did not use the medication that was purchased.

5. Conclusion

Trends in benzodiazepine and other alternative PIM use among older adults changed considerably from 2000 to 2016 in Quebec. While benzodiazepine prevalence decreased, alternative PIM uses increased. Multimorbid individuals were more likely to receive those medications. Such findings highlight the need to address the use of benzodiazepines and alternative PIMs in multimorbid older adults, as those individuals contribute to an increasing demand on the healthcare system. Given the iatrogenic risk induced by benzodiazepines and other PIMs, the burden on the healthcare system may be further exacerbated with the use of such medications. Older adults, especially those with multimorbidity, could thus benefit from interventions to deprescribe benzodiazepines and alternative PIMs, and be provided with non-pharmacological options.

REFERENCES

1. Roberts K, Rao D, Bennett T, Loukine L, Jayaraman G. Prevalence and patterns of chronic disease multimorbidity and associated determinants in Canada. Health promotion and chronic disease prevention in Canada: research, policy, and practice. 2015;35(6):87.
2. Boyd CM, Fortin M. Future of multimorbidity research: how should understanding of multimorbidity inform health system design? Public health reviews. 2010;32(2):451.
3. Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T. Managing patients with multimorbidity: systematic review of interventions in primary care and community settings. Bmj. 2012;345:e5205.
4. Sinnott C, Bradley CP. Multimorbidity or polypharmacy: two sides of the same coin? : SAGE Publications Sage UK: London, England; 2015.
5. Morin L, Fastbom J, Laroche ML, Johnell K. Potentially inappropriate drug use in older people: a nationwide comparison of different explicit criteria for population-based estimates. British journal of clinical pharmacology. 2015;80(2):315-24.
6. Davidoff AJ, Miller GE, Sarpong EM, Yang E, Brandt N, Fick DM. Prevalence of Potentially Inappropriate Medication Use in Older Adults Using the 2012 Beers Criteria. Journal of the American Geriatrics Society. 2015;63:486-500.
7. Roux B, Sirois C, Simard M, Gagnon M-E, Laroche M-L. Potentially inappropriate medications in older adults: a population-based cohort study. Family Practice. 2020;37(2):173-9.
8. Schroeck JL, Ford J, Conway EL, Kurtzhalts KE, Gee ME, Vollmer KA et al. Review of safety and efficacy of sleep medicines in older adults. Clinical therapeutics. 2016;38(11):2340-72.
9. Martin P, Tamblyn R, Ahmed S, Benedetti A, Tannenbaum C. A consumer-targeted, pharmacist-led, educational intervention to reduce inappropriate medication use in community older adults (D-PRESCRIBE trial): study protocol for a cluster randomized controlled trial. Trials. 2015;16(1):266.
10. Tamblyn R, Abrahamowicz M, Berger Rd, McLeod P, Bartlett G. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. Journal of the American Geriatrics Society. 2005;53(2):233-41.

11. Martinez-Cengotitabengoa M, Diaz-Gutierrez MJ, Besga A, Bermúdez-Ampudia C, López P, Rondon MB et al. Benzodiazepine prescriptions and falls in older men and women. Revista de Psiquiatría y Salud Mental (English Edition). 2018;11(1):12-8.
12. Nafti M, Sirois C, Kröger E, Carmichael P-H, Laurin D. Is benzodiazepine use associated with the risk of dementia and cognitive impairment–not dementia in older persons? The Canadian study of health and aging. Annals of Pharmacotherapy. 2020;54(3):219-25.
13. Kroll DS, Nieva HR, Barsky AJ, Linder JA. Benzodiazepines are prescribed more frequently to patients already at risk for benzodiazepine-related adverse events in primary care. Journal of general internal medicine. 2016;31(9):1027-34.
14. Linnet K, Gudmundsson LS, Birgisdottir FG, Sigurdsson EL, Johannsson M, Tomasdottir MO et al. Multimorbidity and use of hypnotic and anxiolytic drugs: cross-sectional and follow-up study in primary healthcare in Iceland. BMC family practice. 2016;17(1):69.
15. Canadian Geriatrics Society. Five things physicians and patients should question. Choosing Wisely Canada Toronto, ON; 2014.
16. Iaboni A, Bronskill SE, Reynolds KB, Wang X, Rochon PA, Herrmann N et al. Changing pattern of sedative use in older adults: a population-based cohort study. Drugs & aging. 2016;33(7):523-33.
17. Kronholm E, Markkula J, Virta LJ. What is behind the seeming cessation of the increase in sleep medicine consumption in Finland during the last years? Journal of public health research. 2012;1(2):149.
18. Maglione M, Maher AR, Hu J, Wang Z, Shanman R, Shekelle PG et al. Off-label use of atypical antipsychotics: an update. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. Centre for Reviews and Dissemination (UK); 2011.
19. Black CD, McCarthy L, Gomes T, Mamdani M, Juurlink D, Tadrous M. Interprovincial variation of psychotropic prescriptions dispensed to older Canadian adults. Canadian Geriatrics Journal. 2018;21(3):269.

20. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. Journal of Clinical Sleep Medicine. 2017;13(02):307-49.
21. Fick DM, Semla TP, Steinman M, Beizer J, Brandt N et al. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society. 2019;67(4):674-94.
22. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. International journal of clinical pharmacology and therapeutics. 2008;46(2):72-83.
23. Blais C, Jean S, Sirois C, Rochette L, Plante C, Larocque I et al. Le Système intégré de surveillance des maladies chroniques du Québec (SISMACQ), une approche novatrice. Maladies Chroniques et Blessures au Canada. 2014;34:247-56.
24. Tamblyn R, Lavoie G, Petrella L, Monette J. 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):999-1009.
25. Simard M, Sirois C, Candas B. Validation of the combined comorbidity index of Charlson and Elixhauser to predict 30-day mortality across ICD-9 and ICD-10. Medical care. 2018;56(5):441-7.
26. Gaulin M, Simard M, Candas B, Lesage A, Sirois C. Combined impacts of multimorbidity and mental disorders on frequent emergency department visits: a retrospective cohort study in Quebec, Canada. CMAJ. CMAJ; 2019;191:E724-32.
27. Petersen MR, Deddens JA. A comparison of two methods for estimating prevalence ratios. BMC medical research methodology. 2008;8(1):9.
28. Alessi-Severini S, Bolton JM, Enns MW, Dahl M, Collins DM, Chateau D et al. Use of benzodiazepines and related drugs in Manitoba: a population-based study. CMAJ open. 2014;2(4):E208.
29. Kurko T, Saastamoinen LK, Tuulio-Henriksson A, Taiminen T, Tiihonen J, Airaksinen M et al. Trends in the long-term use of benzodiazepine anxiolytics and hypnotics: A national register study for 2006 to 2014. Pharmacoepidemiology and drug safety. 2018;27(6):674-82.

30. Brett J, Maust DT, Bouck Z, Ignacio RV, Mecredy G, Kerr EA et al. Benzodiazepine use in older adults in the United States, Ontario, and Australia from 2010 to 2016. Journal of the American Geriatrics Society. 2018;66(6):1180-5.
31. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA psychiatry. 2015;72(2):136-42.
32. Cadogan CA, Ryan C, Cahir C, Bradley CP, Bennett K. Benzodiazepine and Z-drug prescribing in Ireland: analysis of national prescribing trends from 2005 to 2015. British Journal of Clinical Pharmacology. 2018;84(6):1354-63.
33. Davies SJ, Jacob B, Rudoler D, Zaheer J, de Oliveira C, Kurdyak P. Benzodiazepine prescription in Ontario residents aged 65 and over: a population-based study from 1998 to 2013. Therapeutic advances in psychopharmacology. 2018;8(3):99-114.
34. Brandt J, Alessi-Severini S, Singer A, Leong C. Novel measures of benzodiazepine and Z-Drug utilisation trends in a Canadian provincial adult population (2001-2016). Journal of Population Therapeutics and Clinical Pharmacology. 2019;26(1):e22-e38.
35. Nardi AE, Valenca A, Freire RC, Mochcovitch M, Amrein R, Sardinha A et al. Psychopharmacotherapy of panic disorder: 8-week randomized trial with clonazepam and paroxetine. Brazilian Journal of Medical and Biological Research. 2011;44(4):366-73.
36. Nardi A, Machado S, Ferreira Almada L, Paes F, Cardoso Silva A, Jose Marques R et al. Clonazepam for the treatment of panic disorder. Current drug targets. 2013;14(3):353-64.
37. Van Eijk JTM, Bosma H, Jonkers C, Lamers F, Muijrers PE. Prescribing antidepressants and benzodiazepines in the Netherlands: is chronic physical illness involved? Depression research and treatment. 2010;2010.
38. DeJean D, Giacomini M, Vanstone M, Brundisini F. Patient experiences of depression and anxiety with chronic disease: a systematic review and qualitative meta-synthesis. Ontario health technology assessment series. 2013;13(16):1.
39. De Beurs E, Beekman A, Geerlings S, Deeg D, Van Dyck R, Van Tilburg W. On becoming depressed or anxious in late life: similar vulnerability factors but different effects of stressful life events. The British Journal of Psychiatry. 2001;179(5):426-31.

40. Patten SB. Long-term medical conditions and major depression in a Canadian population study at waves 1 and 2. Journal of affective disorders. 2001;63(1-3):35-41.
41. Garcia ME. Capsule Commentary on Kroll et al., Benzodiazepines are prescribed more frequently to patients already at risk for benzodiazepine-related adverse events in primary care. Journal of general internal medicine. 2016;31(9):1078-.
42. Liu X, Ye W, Watson P, Tepper P. Use of benzodiazepines, hypnotics, and anxiolytics in major depressive disorder: association with chronic pain diseases. The Journal of nervous and mental disease. 2010;198(8):544-50.
43. Thorell K, Ranstad K, Midlöv P, Borgquist L, Halling A. Is use of fall risk-increasing drugs in an elderly population associated with an increased risk of hip fracture, after adjustment for multimorbidity level: a cohort study. BMC geriatrics. 2014;14(1):131.
44. Linnet K, Sigurdsson JA, Tomasdottir MO, Sigurdsson EL, Gudmundsson LS. Association between prescription of hypnotics/anxiolytics and mortality in multimorbid and non-multimorbid patients: a longitudinal cohort study in primary care. BMJ open. 2019;9(12).
45. Díaz-Gutiérrez MJ, Martínez-Cengotitabengoa M, Sáez de Adana E, Cano AI, Martínez-Cengotitabengoa MT, Besga A, et al. Relationship between the use of benzodiazepines and falls in older adults: A systematic review. Maturitas. juill 2017;101:17-22.
46. Finkle WD, Der JS, Greenland S, Adams JL, Ridgeway G, Blaschke T, et al. Risk of Fractures Requiring Hospitalization After an Initial Prescription for Zolpidem, Alprazolam, Lorazepam, or Diazepam in Older Adults. Journal of the American Geriatrics Society. 2011;59(10):1883-90.

TABLES

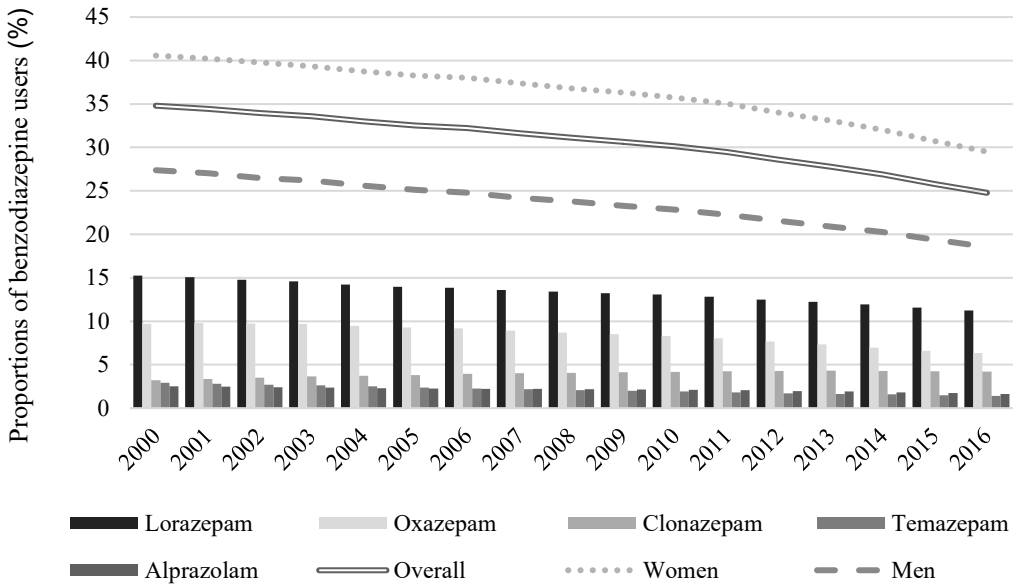
Table 1. Characteristics of people 66 years and older from 2000* to 2016, in the province of Quebec (Canada)

Years	Quebec population aged 66 and older					Benzodiazepine users						
	Total population (N)	Mean age	Sex ratio (F/M)	Mean number of chronic diseases	Proportion of multimorbidity (%)	Number of users (n)	Age-standardized proportion of users (%; 95% CI)			Mean age	Mean number of chronic diseases	Age- and sex-standardized proportion of multimorbid individual that are benzodiazepine users (%; 95%CI)
							Total (age- and sex-standardized)	Men	Women			
2000	779 667	75.44	1.45	1.97	48.5	275 139	34.8 (34.6-35.0)	27.4	40.6	76.32	2.50	43.3 (43.0-43.6)
2001	793 691	75.57	1.44	2.04	49.6	277 642	34.4 (34.3-34.6)	27.0	40.2	76.48	2.58	42.6 (42.4-42.0)
2002	806 587	75.69	1.44	2.09	50.4	278 522	33.9 (33.8-34.1)	26.5	39.8	76.61	2.65	41.8 (41.5-42.1)
2003	818 396	75.83	1.43	2.12	50.9	280 089	33.6 (33.4-33.7)	26.2	39.3	76.77	2.68	41.2 (40.9-41.1)
2004	831 274	75.94	1.42	2.14	51.1	279 826	33.0 (32.8-33.2)	25.6	38.7	76.91	2.70	40.4 (40.1-40.6)
2005	847 736	76.02	1.41	2.15	51.2	281 352	32.5 (32.4-32.7)	25.1	38.3	77.02	2.70	39.6 (39.3-39.8)
2006	866 259	76.12	1.40	2.16	51.3	285 091	32.2 (32,1-32,4)	24.8	38.0	77.14	2.71	39.1 (38.8-39.3)
2007	887 083	76.18	1.39	2.15	51.1	286 490	31.6 (31.5-31.8)	24.2	37.4	77.23	2.69	38.3 (38.0-38.5)
2008	911 361	76.22	1.37	2.14	50.8	289 577	31.1 (31.0-31.3)	23.8	36.8	77.29	2.67	37.7 (37.4-37.9)
2009	938 181	76.23	1.36	2.12	50.4	293 117	30.6 (30.5-30.8)	23.3	36.3	77.33	2.66	37.1 (36.9-37.3)
2010	967 681	76.22	1.34	2.12	49.9	296 992	30.1 (30.0-30.3)	22.9	35.7	77.36	2.65	36.6 (36.3-36.8)
2011	1 000 911	76.19	1.33	2.12	49.4	299 870	29.5 (29.3-29.6)	22.3	35.0	77.36	2.67	35.9 (35.6-36.1)
2012	1 038 114	76.17	1.31	2.13	49.0	301 344	28.6 (28.5-28.7)	21.5	34.0	77.39	2.70	34.8 (34.6-35.0)
2013	1 078 554	76.11	1.30	2.12	48.4	303 445	27.8 (27.6-27.9)	20.9	33.1	77.38	2.70	33.9 (33.6-34.1)
2014	1 120 024	76.07	1.28	2.11	47.8	304 489	26.9 (26.8-27.0)	20.2	32.0	77.39	2.71	32.9 (32.7-33.2)
2015	1 159 839	76.04	1.25	2.10	47.1	301 901	25.8 (25.7-25.9)	19.4	30.7	77.39	2.70	31.7 (31.5-31.9)
2016	1 202 705	76.05	1.26	2.08	46.3	300 400	24.8 (24.7-24.9)	18.6	29.5	77.44	2.68	30.6 (30.4-30.8)

***Years 2000 refers to the period studied from April 1st 2000 to March 31st 2001, as for the subsequent years.**

FIGURES

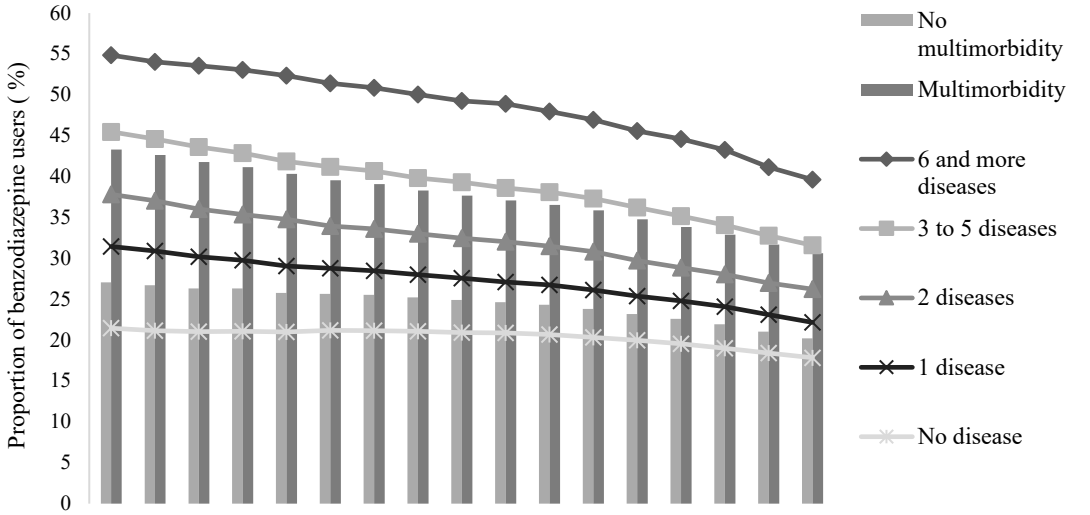
Figure 1. Standardized proportions of benzodiazepine users between 2000 and 2016 among people 66 years and older in the province of Quebec (Canada)[1]



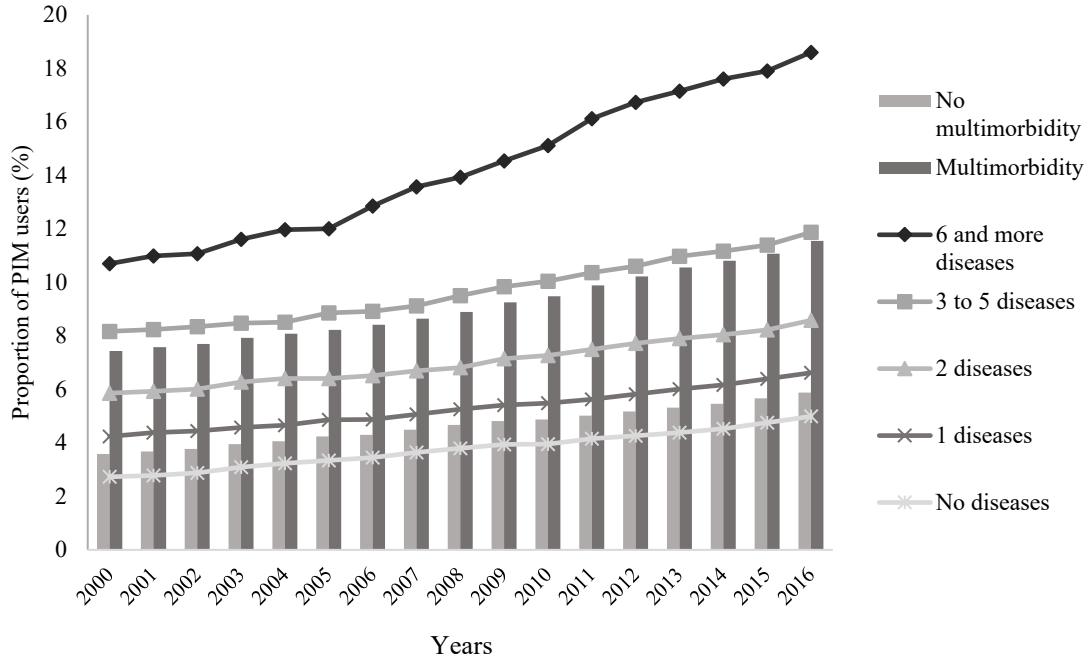
[1] Overall proportions are age- and sex-standardized, while proportions for women and men are age-standardized. Confidence interval being very narrow, they are not shown in figure

Figure 2. Age- and sex-standardized proportions of benzodiazepine (a) and alternative potentially inappropriate medication (PIM) (b) users between 2000 and 2016 among people 66 years and older in the province of Quebec (Canada), according to multimorbidity[1]

a)

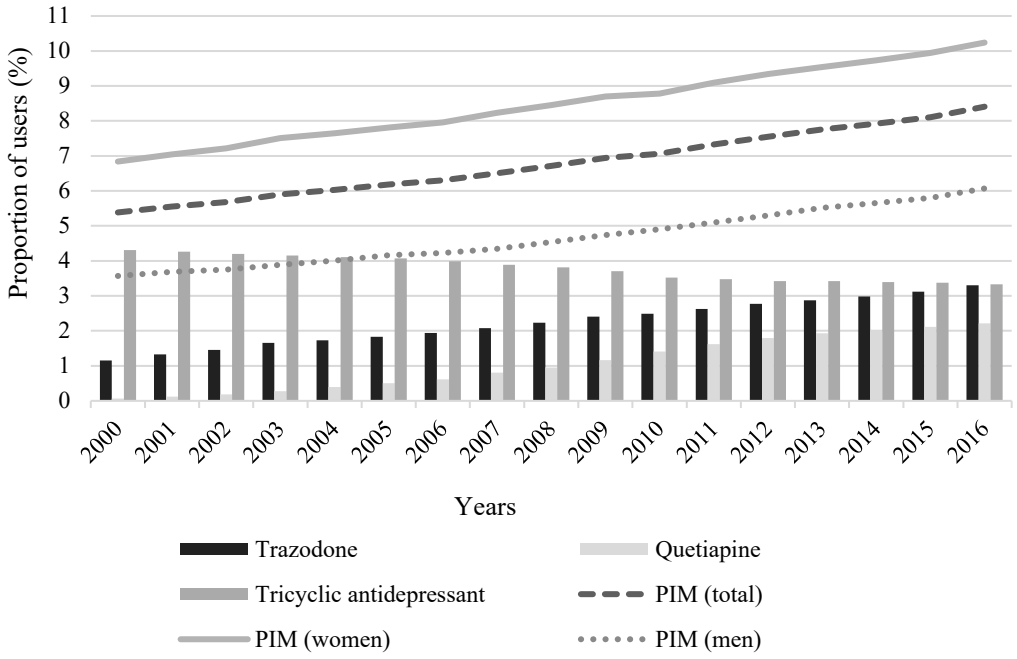


b)



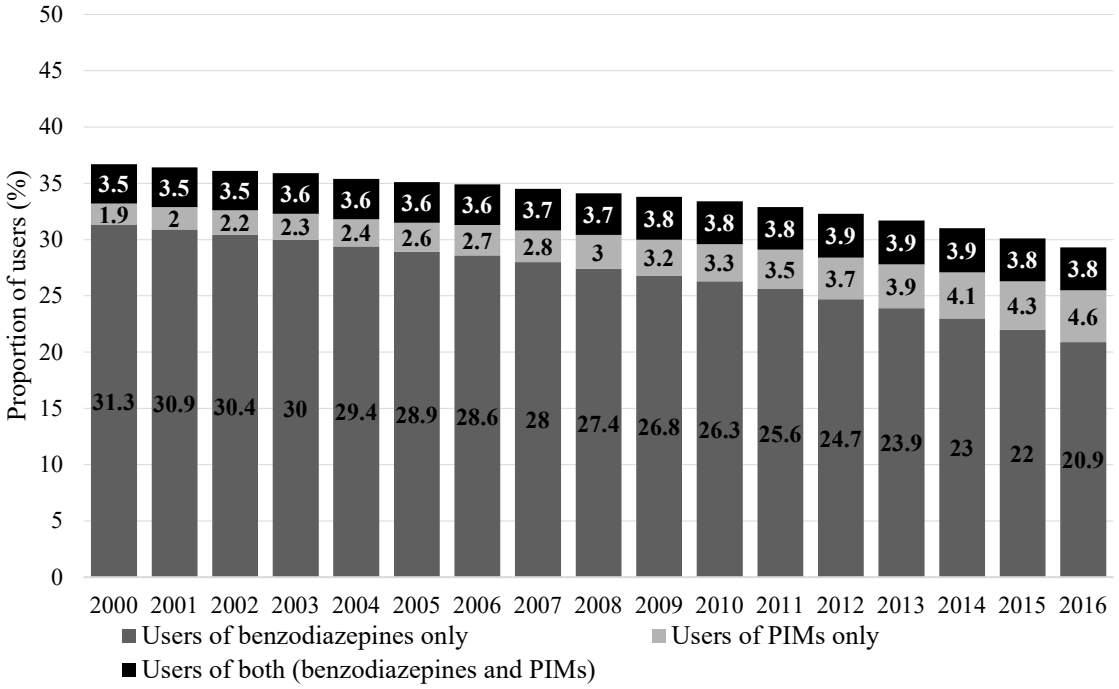
[1]Confidence interval being very narrow, they are not shown in the figures

Figure 3. Standardized proportions of alternative PIM users between 2000 and 2016 among people 66 years and older in the province of Quebec (Canada) [1]



[1] Overall proportions are age- and sex-standardized, while proportions for women and men are age-standardized. Confidence interval being very narrow, they are not shown in figure

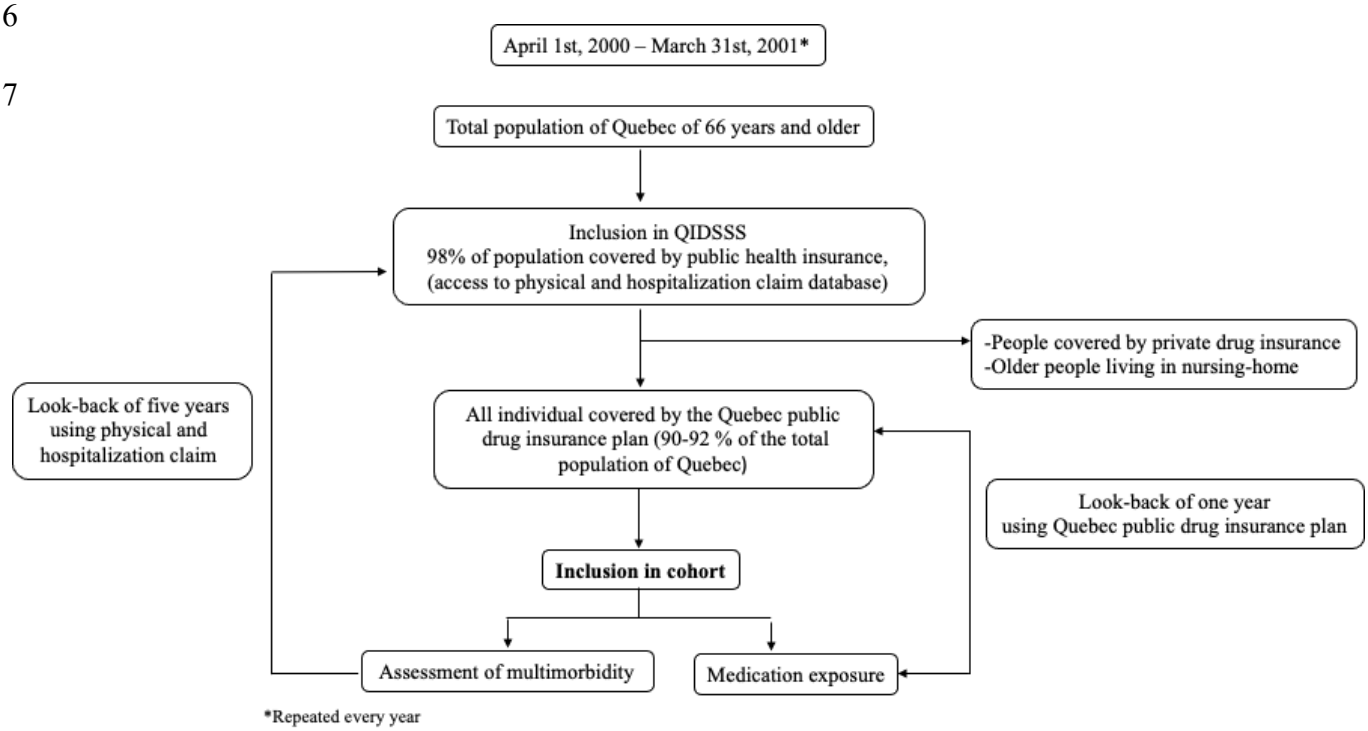
Figure 4. Age- and sex-standardized proportions of users of benzodiazepines, alternative PIMs [1], and both of them between 2000 and 2016 among people 66 years and older in the province of Quebec (Canada)[2]



[1] Alternative PIMs include quetiapine (25 mg or less), tradozone and tricyclic antidepressants
[2]Confidence interval being very narrow, they are not shown in the figure

APPENDIX 1

Flow Chart of the Study Population



APPENDIX 2

Table A1. Benzodiazepines and alternative potentially inappropriate medications covered by the Quebec public drug plan that are included in the study

Benzodiazepines	Potentially inappropriate medications
Alprazolam	**Antipsychotic**
Bromazepam	Quetiapine (25mg or less)
Clorazepate	
Chlordiazepoxide	**Tricyclic Antidepressants**
Clobazam	Amitryptiline
Clonazepam	Desipramine
Diazepam	Doxepin
Flurazepam	Imipramine
Lorazepam	Nortriptyline
Nitrazepam	Trimipramine
Oxazepam	
Temazepam	**Other antidepressants**
Triazolam	Trazodone

APPENDIX 3

Table A2. List of the 31 comorbidities from the Combined Comorbidity Index included in the count of diseases

List of Comorbidities	
AIDS/HIV	Hypothyroidism
Alcohol abuse	Liver diseases
Anemia	Metastatic cancer
Any tumor without metastasis	Myocardial infarction
Cardiac arrhythmias	Neurological disorders
Cerebrovascular diseases	Obesity
Chronic pulmonary diseases	Paralysis
Coagulopathy	Peripheral vascular disorders
Congestive heart failure	Psychosis
Dementia	Pulmonary heart diseases
Depression	Renal diseases
Diabetes, complicated	Rheumatoid arthritis/collagen vascular diseases
Diabetes, uncomplicated	Ulcer disease
Drug abuse	Valvular diseases
Fluid and electrolyte disorders	Weight loss
Hypertension	

APPENDIX 4

Table A3. Benzodiazepine users between 2000 and 2016 among individuals aged 66 years and over covered by the prescription drug insurance plan for the whole year, in the province of Quebec (Canada)[1]

Total population		Benzodiazepine users	
Year[2]	Population	Number of users	Age- and sex-standardized proportion of benzodiazepine users (95% CI)
2000	753 247	263 048	34.4 (34.3-34.6)
2001	766 551	265 376	34.1 (33.9-34.3)
2002	779 630	266 372	33.6 (33.4-33.8)
2003	790 219	267 326	33.2 (33.1-33.4)
2004	803 217	267 169	32.6 (32.5-32.8)
2005	821 240	269 613	32.2 (32.0-32.4)
2006	838 331	272 535	31.9 (31.7-32.0)
2007	858 982	274 236	31.3 (31.1-31.5)
2008	882 596	276 944	30.8 (30.6-30.9)
2009	908 907	280 294	30.3 (30.1-30.4)
2010	936 911	283 559	29.8 (29.6-29.9)
2011	970 032	286 525	29.1 (28.9-29.2)
2012	1005435	287 583	28.2 (28.1-28.4)
2013	1046471	290 051	27.4 (27.3-27.6)
2014	1084747	290 019	26.5 (26.4-26.7)
2015	1125783	288 120	25.4 (25.3-25.6)
2016	1167102	286 409	24.4 (24.3-24.5)

[1] Patients who died and those transferred to long-term care were thus excluded

[2]Years 2000 refers to the period studied from April 1st 2000 to March 31st 2001, as for the subsequent years.

APPENDIX 5

Figure A1. Age- and sex-standardized proportions of benzodiazepine users between 2000 and 2016 among people 66 years and older in the province of Quebec (Canada), according to the Combined Comorbidity Index score

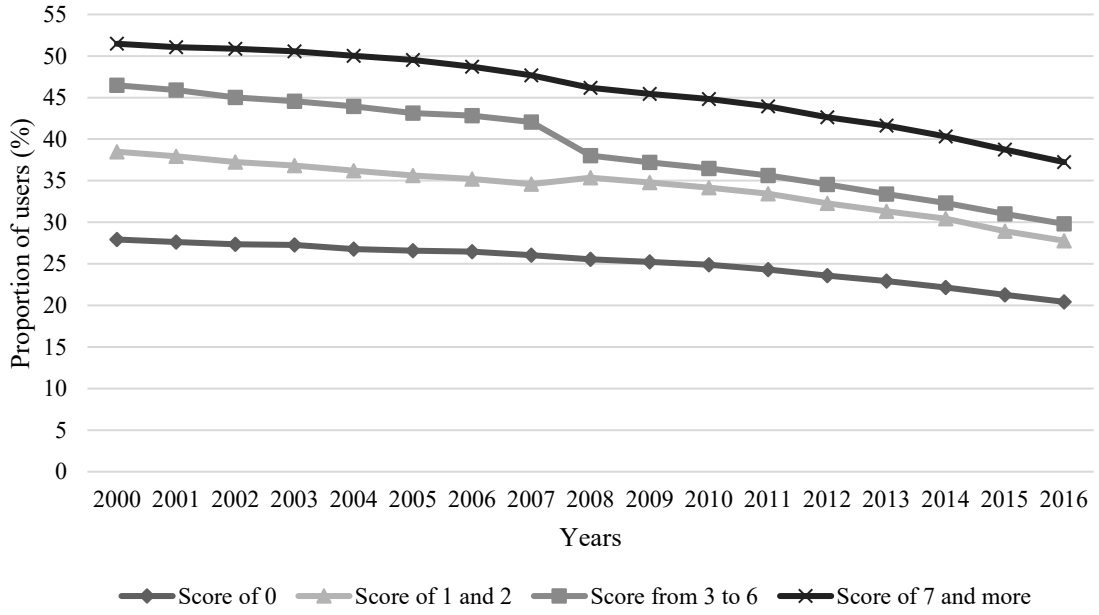
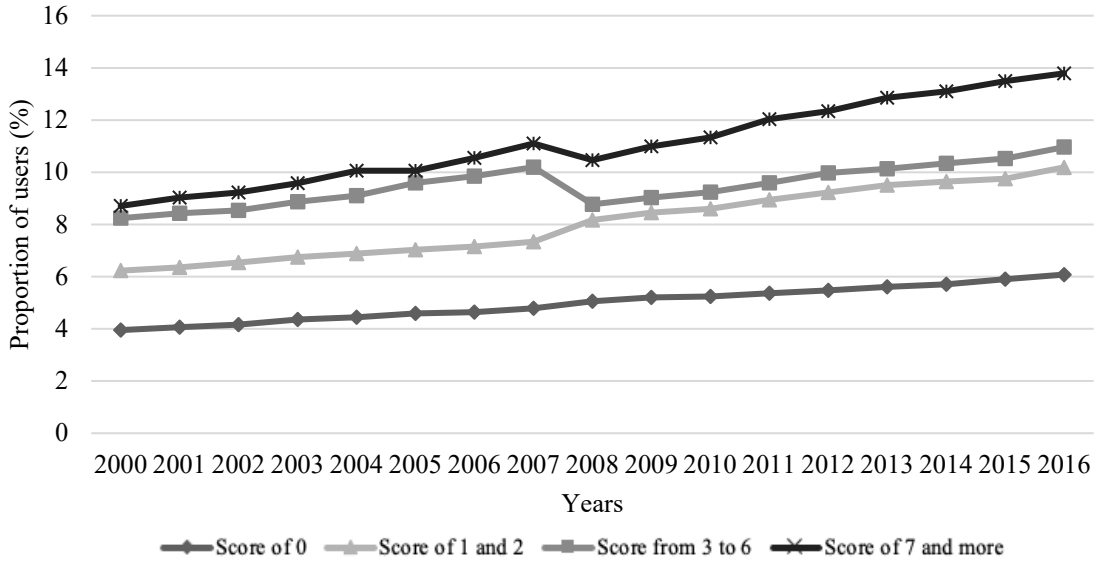


Figure A2. Age- and sex-standardized proportions of alternative potentially inappropriate medication[1] (PIM) users between 2000 and 2016 among people 66 years and older in the province of Quebec (Canada), according to the Combined Comorbidity Index score



[1]Alternative PIMs include quetiapine (25 mg or less), tradozone and tricyclic antidepressants