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

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1 **Trends in benzodiazepine and alternative hypnotic use in relation with multimorbidity**
2 **among older adults in Quebec, Canada**
3

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21 **Conflict of interest**

22 The authors have no conflict of interest to declare.

23 **Availability of data and material**

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

1

2 **Code availability**

3 Not applicable

4 **Author's contribution**

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

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12 their valuable assistance during the research.

1 **Abstract:**

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

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

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

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

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

21

22

23

1 **Key points:**

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

11

12 **Keywords** : Benzodiazepines, Hypnotics, Potentially Inappropriate Medications, Multimorbidity

1 **1. Background**

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

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

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

26 **2. Methods**

1 2.1 Design and setting

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

15 2.2 Study population

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

21 2.3 Medication exposure

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

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

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

13 2.4 Multimorbidity assessment

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

22 2.5 Statistical analysis

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

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

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

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

11 2.6 Ethics approval

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

15 3. Results

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

19 3.1 Benzodiazepine trends and multimorbidity

20 The adjusted proportion of individuals aged 66 and older that received at least one benzodiazepine decreased
21 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
22 prevalence: -1.9% per year, p-value for trend < 0.0001). This represents an absolute decrease of about 10%
23 in the proportion of users over the 17 years. This decline in the proportion of users was observed for all
24 benzodiazepines except for clonazepam where the proportion increased slightly from 3.2% [3.2-3.3] to 4.2%
25 [4.1-4.2] (Figure 1). Lorazepam was the most prescribed benzodiazepine every year, with 15.3% [15.1-15.4]

1 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])
2 (Figure 1). The prevalence of benzodiazepine users was persistently higher in women than in men (Figure
3 1), but the gap between sexes appeared to narrow over time. In 2000, 40.6% [40.3-40.8] of women claimed
4 at least one prescription, compared to 27.4% [27.1-27.6] of men. The proportions decreased in 2016 to 29.5%
5 [29.3-29.7] for women and 18.5% [18.4-18.7] for men, respectively.

6 People with multimorbidity were at consistently higher risk of using a benzodiazepine each year (Figure 2a).
7 In 2000, 43.3% [43.0-43.6] of multimorbid older adults received at least one benzodiazepine while the
8 corresponding proportion was 27.1% [26.8-27.3] among individuals without multimorbidity. Both
9 proportions decreased in the 17 years studied, with 30.6% [30.4-30.8] and 20.2% [20.1-20.4] of individuals
10 with and without multimorbidity using benzodiazepines in 2016, respectively. Likewise, benzodiazepine use
11 was more common as the number of chronic diseases increased. In 2000, 54.9% [53.9-55.8] of older
12 individuals with six and more chronic diseases had at least one benzodiazepine claim, compared to 21.5%
13 [21.2-21.8] of older individuals with no chronic diseases. The respective proportions were 39.6% [39.1-40.2]
14 and 17.9% [17.6-18.1] in 2016. Those with six and more chronic diseases have nonetheless experienced the
15 greatest absolute drop in use over the period: 15.3% (from 54.9% to 39.6%), while the same proportion
16 declined by 3.7% (from 21.5% to 17.8%) among individuals without chronic disease.

17 3.2 Alternative PIM trends and multimorbidity

18 ~~Parallel to the decline in benzodiazepine use,~~ Alternative PIM use increased from 5.4% [99% CI: 5.3-5.5] in
19 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-
20 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-
21 3.4]. Overall, the risk of receiving an alternative PIM of any type increased by 1.03% each year (p for trend
22 <0.0001). Women were greater users of alternative PIMs than men. For example, the proportion of users
23 were 10.2% and 6.1% in 2016, respectively. However, the proportion of users of all types of studied
24 medications combined (both benzodiazepines and/or alternative PIMs) decreased over the 17-year study
25 period, from 36.7% [36.6-36.9] to 29.4% [29.2-29.5] (Figure 4). On the absolute scale, the proportion of
26 users who were dispensed only benzodiazepines decreased by 10.4% while the proportion of users who used

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

3 Individuals with multimorbidity were at higher risk of using at least one alternative PIM. In 2016, 11.6%
4 [11.4-11.7] of individuals with multimorbidity were users of alternative PIMs, whereas 5.9% [5.8-6.0] of
5 individuals with no multimorbidity were using them. Individuals with six chronic diseases and more
6 experienced the largest absolute increase in use between 2000 and 2016 (7.9%, from 10.7 % to 18.6%)
7 compared to those without chronic diseases (2.3%, from 2.7% to 5.0%) (Figure 2b).

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

15 **4. Discussion**

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

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

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

5 Of all the alternative PIMs selected, only trazodone and quetiapine showed a progressive increase in the
6 proportion of users over time. Nonetheless, the total use of alternative PIMs increased from 5.4% to 8.4%.
7 In Ontario, Iaboni and al. previously documented a similar pattern for these two medications from 2002 to
8 2013 [16]. Multimorbid individuals were the largest users of benzodiazepines and alternative PIMs. They
9 might also be more likely to be dual users of both PIMs and benzodiazepines. Those findings are consistent
10 with previous studies conducted on multimorbidity and hypnotic use. In Iceland, a study revealed that among
11 individuals of all ages who were prescribed hypnotic medications, 85% were considered multimorbid,
12 making multimorbidity a significant risk factor for the use of hypnotic medications (OR=14.9; 95%CI 14.4-
13 15.4) [14]. In addition, Van Eijk et al. documented a relationship between benzodiazepine use and
14 multimorbidity in their cohort study in the Netherlands; the risk of receiving a benzodiazepine was increased
15 for both older multimorbid men (OR: 1.40; 95% CI:1.36-1.44) and women (1.46;1.40-1.52) [37].
16 Multimorbid individuals were also more likely to repeat prescriptions [37]. Some hypotheses can be made to
17 explain why multimorbid individuals are more at risk of being prescribed benzodiazepines and other
18 alternative PIMs. On one hand, multimorbidity is closely related to polypharmacy, as the treatment of chronic
19 diseases often requires the use of simultaneous different drugs, and polypharmacy is an important risk factor
20 for being prescribed a PIM [5]. Yet such logic is probably insufficient to explain the relation observed.
21 Among individuals with chronic physical illness, the prevalence of mental health problems such as depression
22 or anxiety is high [37-40]. Treatment of those patients seems to be different, and it was suggested that
23 depressed people with comorbidities were more likely to be prescribed benzodiazepines than depressed
24 people with no other conditions [37]. This situation might denote the high complexity clinicians face when
25 dealing with both mental and physical health conditions [41]. Benzodiazepine and alternative PIMs use has
26 also been demonstrated to be more prevalent in people with physical illnesses, including chronic pain,
27 pulmonary diseases, osteoporosis [13,37,42]. Given their diseases, those patients are already more at risk of

1 harm from benzodiazepines and alternative PIMs, such as a hip fracture [13,43]. Furthermore, among people
2 with a larger number of chronic diseases, a greater proportion uses a higher dosage of hypnotic medications
3 [44]. Long-term hypnotic users (both multimorbid and non-multimorbid) also seem to experience a higher
4 risk for mortality, which increases along with dosage [44]. These facts highlight the problematic nature of
5 benzodiazepine and alternative PIM use, particularly among multimorbid people, and support the importance
6 of heightened attention when prescribing benzodiazepine to vulnerable populations. Considering that 30.6%
7 of multimorbid individuals were using benzodiazepines and 11.6% were using other alternative PIMs in 2016
8 in our study, it appears paramount to address this issue.

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

1 7.5% each year), but our results may not be generalizable to this group [23]. Furthermore, the pharmaceutical
2 database does not capture medications dispensed during hospitalization. However, our study aimed to assess
3 community use only, so inpatient use would not have been included in the analysis. We did not assess the
4 doses or the duration of treatments. Although the risks associated with the use of benzodiazepines increase
5 with longer use, higher doses, and longer half-life, there are also adverse events associated with short-term
6 use or the initiation of therapy, such as falls [45,46]. Consequently, we thought that even a single dispensation
7 in an individual would be relevant to draw up a population portrait of benzodiazepine use. Future research
8 should address those aspects to better define the associated risks. Finally, as this study capture medication
9 claims, some individuals considered exposed to the medication might not be exposed if they did not use the
10 medication that was purchased.

11 **5. Conclusion**

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

20

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1 TABLES

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

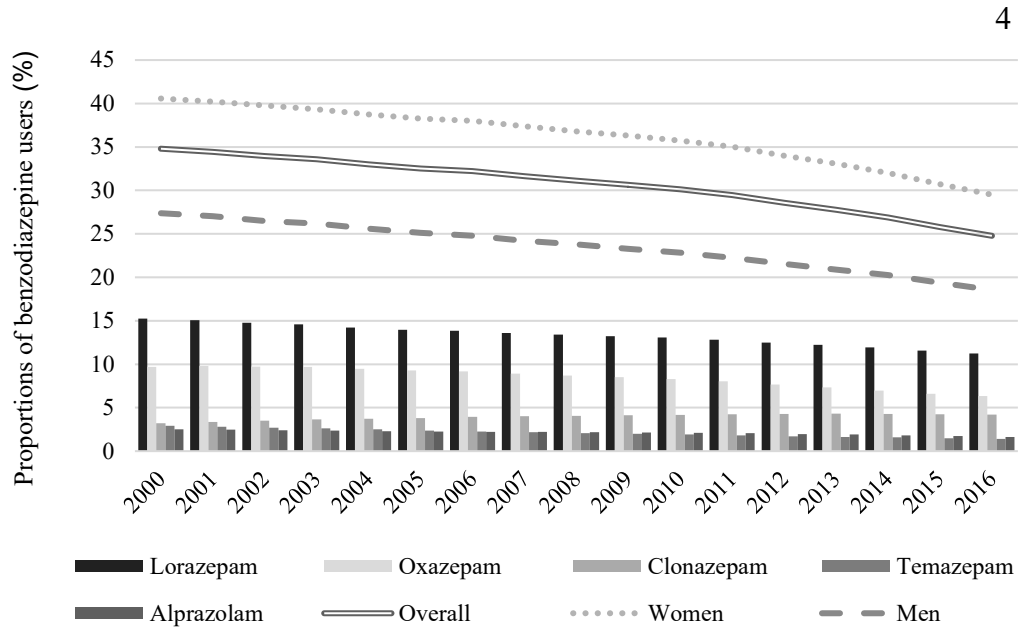
Years	Quebec population aged 66 and older					Benzodiazepine users						
	Total population (N)	Mean age	Sex ratio (F/M)	Mean number of chronic diseases	Proportion of multimorbidity (%)	Number of users (n)	Age-standardized proportion of users (%; 95% CI)			Mean age	Mean number of chronic diseases	Age- 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.

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1 **FIGURES**

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

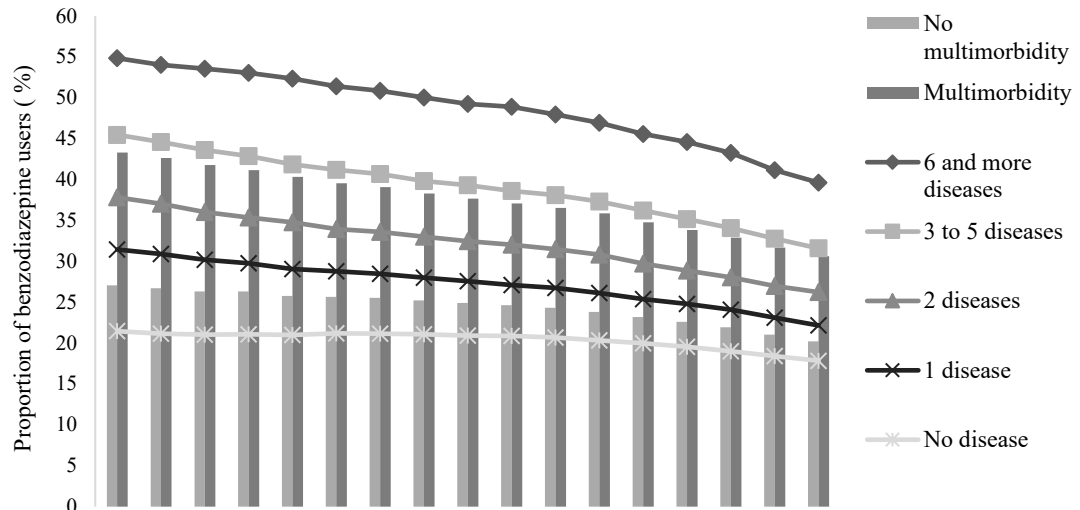


¹ Overall proportions are age- and sex-standardized, while proportions for women and men are age-standardized. Confidence interval being very narrow, they are not shown in figure

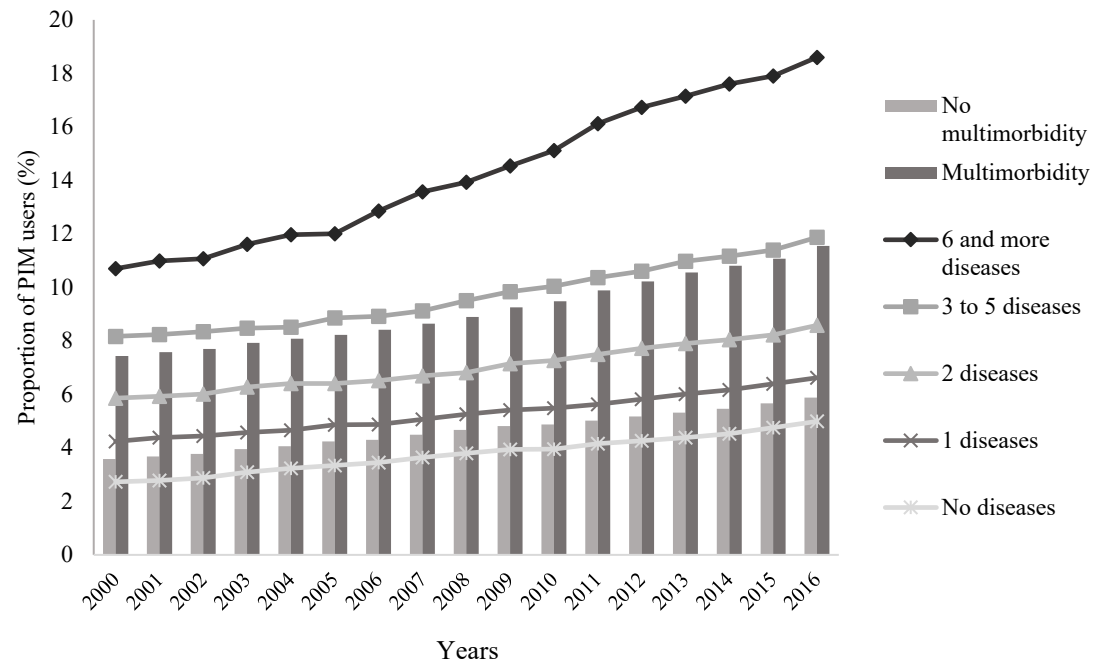
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1 **Figure 2. Age- and sex-standardized proportions of benzodiazepine (a) and alternative potentially**
 2 **inappropriate medication (PIM) (b) users between 2000 and 2016 among people 66 years and older in**
 3 **the province of Quebec (Canada), according to multimorbidity¹**
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6 **a)**



23 **b)**

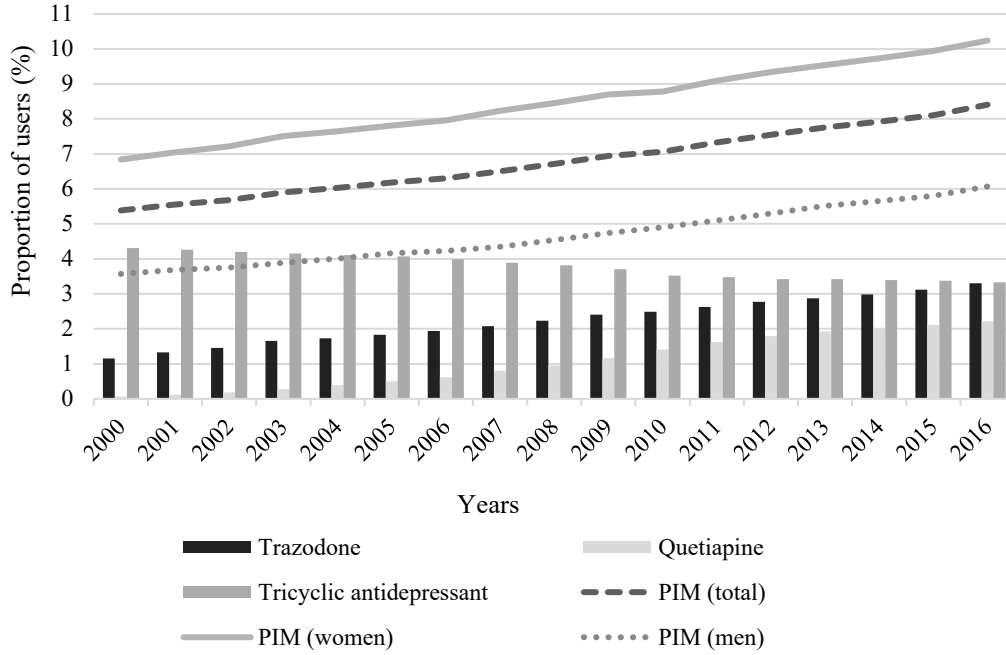


41 ¹Confidence interval being very narrow, they are not shown in the figures

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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

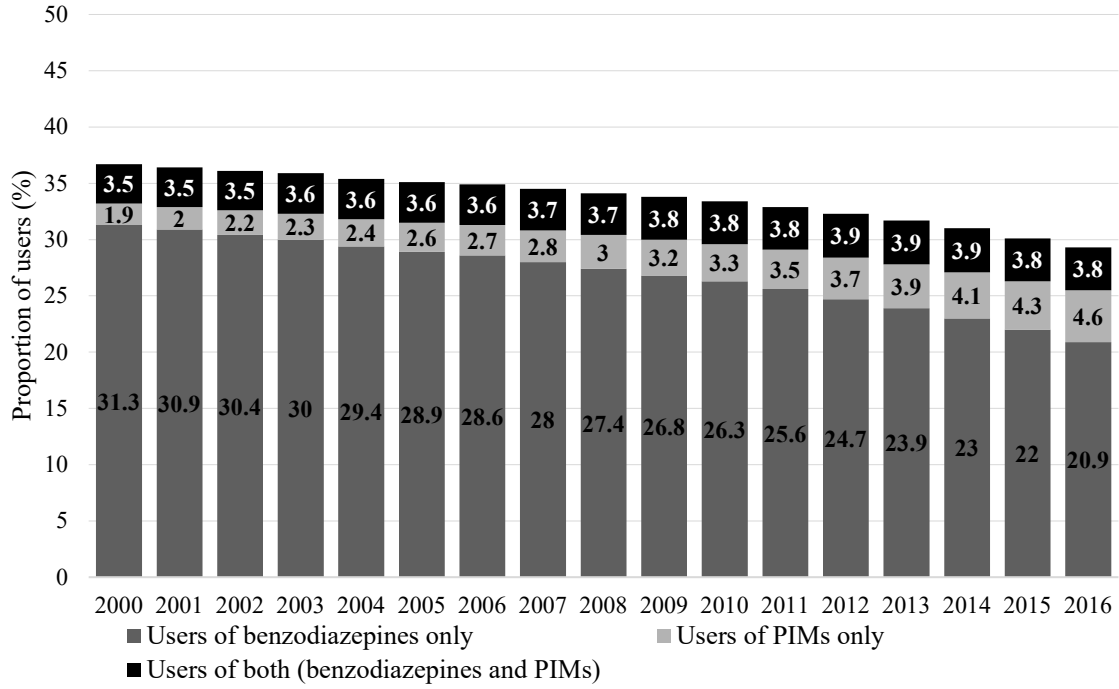


¹ Overall proportions are age- and sex-standardized, while proportions for women and men are age-standardized. Confidence interval being very narrow, they are not shown in figure

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Figure 4. Age- and sex-standardized proportions of users of benzodiazepines, alternative PIMs¹, and both of them between 2000 and 2016 among people 66 years and older in the province of Quebec (Canada)²



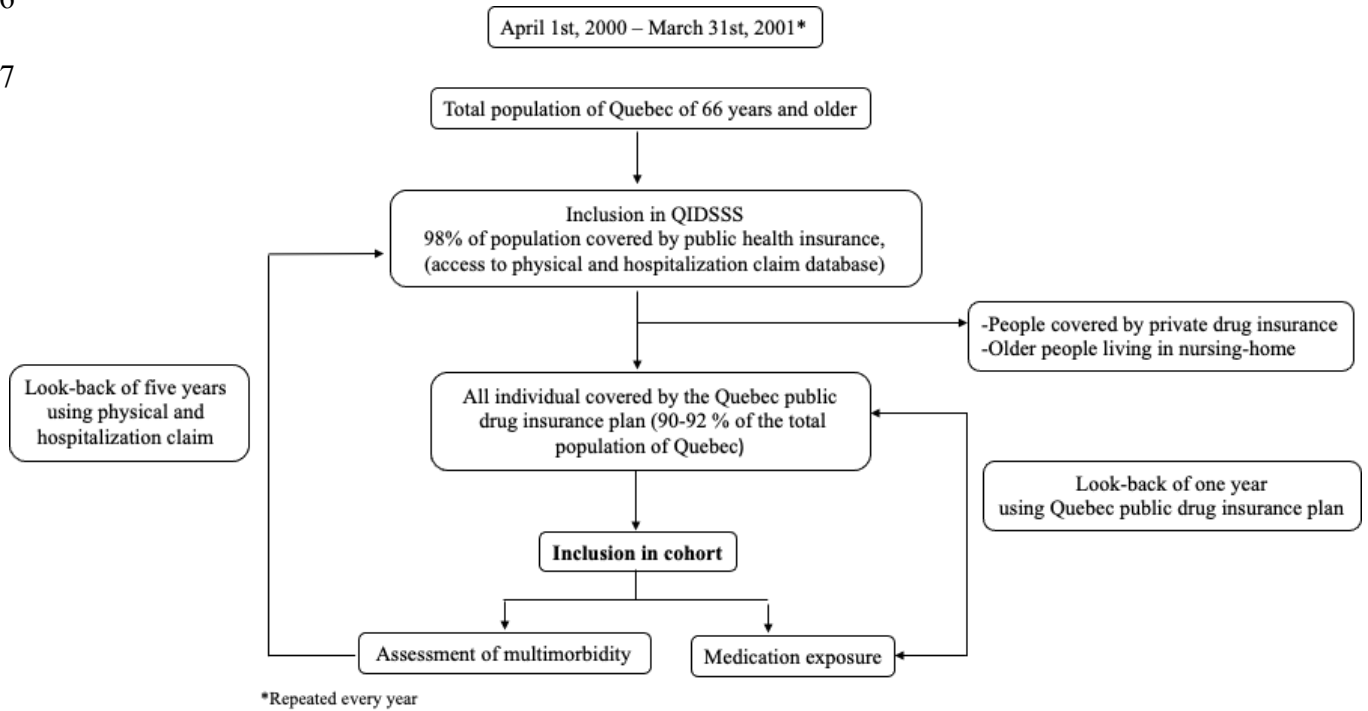
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¹ Alternative PIMs include quetiapine (25 mg or less), tradozone and tricyclic antidepressants
²Confidence interval being very narrow, they are not shown in the figure

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APPENDIX 1

Flow Chart of the Study Population



1 APPENDIX 2

2 Table A1. Benzodiazepines and alternative potentially inappropriate medications covered by the
3 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	Amitriptyline
Clonazepam	Desipramine
Diazepam	Doxepin
Flurazepam	Imipramine
Lorazepam	Nortriptyline
Nitrazepam	Trimipramine
Oxazepam	
Temazepam	Other antidepressants
Triazolam	Trazodone

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1 **APPENDIX 3**

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

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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	

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1 APPENDIX 4

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

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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)

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

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

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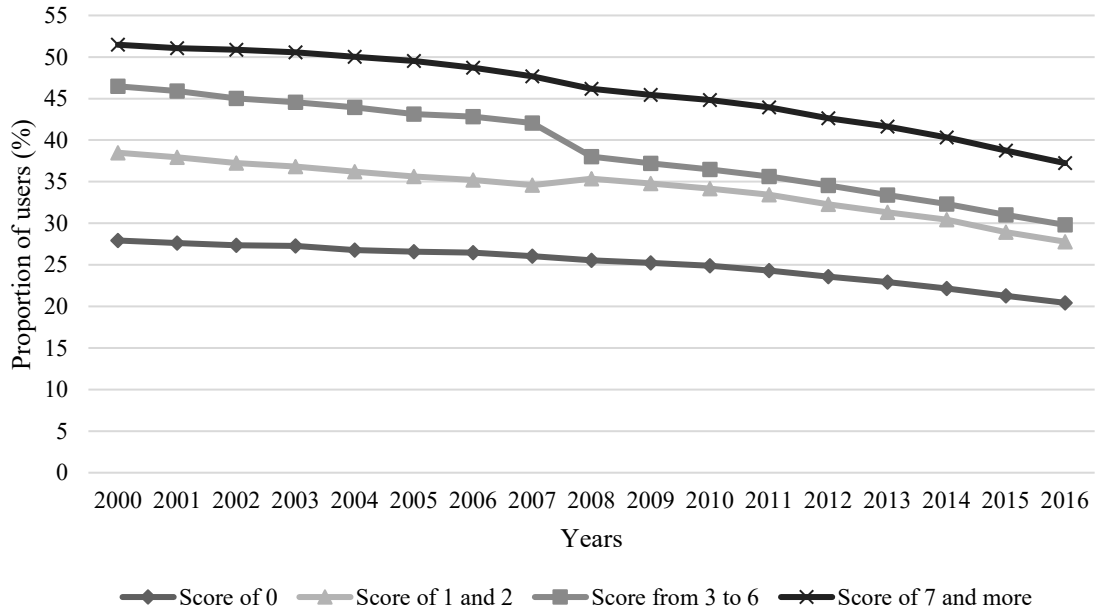
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1 APPENDIX 5

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

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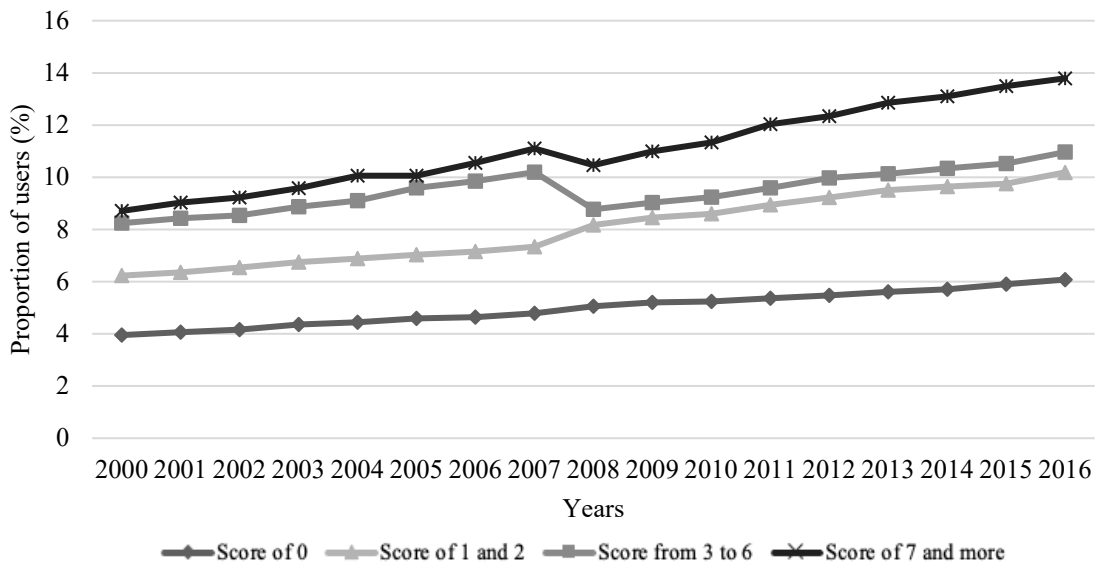


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9 **Figure A2. Age- and sex-standardized proportions of alternative potentially inappropriate**
 10 **medication¹ (PIM) users between 2000 and 2016 among people 66 years and older in the province of**
 11 **Quebec (Canada), according to the Combined Comorbidity Index score**

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¹Alternative PIMs include quetiapine (25 mg or less), trazodone and tricyclic antidepressants