Title page

Benzodiazepine use in older adults in the U.S., Ontario and Australia from 2010 to 2016.

Benzodiazepines in older adults

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IMPACT STATEMENT

We certify that this work is novel. We have used a harmonized study protocol to measure annual incident and prevalent benzodiazepine use in older adults across three jurisdictions – the U.S. (veterans population), Ontario and Australia – from 2010 to 2016. The currency of this study relates to the nomination of this practice as a top priority by the global Choosing Wisely campaign. We are not aware of any studies measuring benzodiazepine use in the elderly on a jurisdictional level since the start of the Choosing Wisely campaign. Employing large datasets and a standardized protocol facilitates comparisons of trends in this practice at a population level. We hope the modest decreases in incidence and prevalence demonstrated here will galvanise clinicians and policy makers to take action to make further reductions.

ABSTRACT

Background: The international medical community has repeatedly called attention to the harms resulting from benzodiazepine use in older adults, yet use persists and is in fact highest among older adults. The global Choosing Wisely campaign has generated renewed momentum to redress this prescribing practice.

Objectives: To detail annual trends in benzodiazepine incidence and prevalence in older adults between 2010 and 2016 across three health jurisdictions.

Design: Observational multi-jurisdictional cohort study with harmonized study protocol.

Setting: The United States (U.S. (veterans population)); Ontario, Canada; and Australia.

Participants: All beneficiaries ≥ 65 years of age (8,270,000 people).

Measurements: Annual incidence and prevalence of benzodiazepine use stratified by age group (65-74, 75-84 and 85+ years) and sex. We performed multiple regression analyses to assess whether rates of incident and prevalent use changed significantly over time.

Results: Over the study period, we observed a significant decrease in incident benzodiazepine use in the U.S. (2.6% to 1.7%) and Ontario (6.0% to 4.4%) but not in Australia (7.0% to 6.7%). We found significant declines in prevalent use in all jurisdictions, (9.2% to 7.3% in the U.S, 18.2% to 13.4% in Ontario and 20.2% to 16.8% in Australia). While incidence and prevalence increased with age in Ontario and Australia, they decreased with advancing age in the U.S. Incidence and prevalence was higher among women in all jurisdictions.

Conclusion: Consistent with other international studies, there have been small but significant reductions in the incidence and prevalence of benzodiazepine use in older adults across all three jurisdictions, with the exception of incidence in Australia. However, use remains inappropriately high – particularly in those 85 and older – and this warrants further attention from clinicians and policy makers.

Key Words: Benzodiazepines, older adults, Choosing Wisely, Australia, Ontario, United States.

INTRODUCTION

Benzodiazepine use in older adults has been associated with a number of harms including increased risk of falls, hip fracture, impaired cognition, all-cause mortality, overdose, and substance use disorder (1-5). As a result, the American Geriatrics Society Beers Criteria and STOPP/START Screening Tools for Geriatric Medicine advise to avoid benzodiazepine use in older adults (6, 7). Most recently, this potentially inappropriate prescribing has been addressed by the Choosing Wisely (CW) International campaign (8), as well as by country-specific CW programs in the United States (U.S.), Canada, and Australia (9-12). Despite this, rates of new and continuing benzodiazepine use in older adults remain higher than in younger age groups (13, 14).

Benzodiazepine use in older adults has been previously described in the U.S., Canada, and Australia (13-16), as well as in several European countries (17). However, differing data sources, methods and time periods make comparisons between studies challenging. Moreover, most studies have not been population-based or have used episode rather than person-level data, impeding analysis of patterns of individual use. In addition, there have been no studies detailing the extent of this low-value practice across multiple jurisdictions since the start of the Choosing Wisely Campaign.

The aim of this study is to detail trends in annual benzodiazepine incidence and prevalence in older adults from 2010 to 2016 using a common methodology across three jurisdictions: the U.S., Ontario, and Australia.

METHODS

Study settings and data

We used prescription claims data from three jurisdictions for this observational study: 1) the Veterans Health Administration of the U.S. Department of Veterans Affairs (VA); 2) the Ontario Drug Benefit (ODB) program; and 3) the Australian Pharmaceutical Benefits Scheme (PBS). Each of these three systems capture prescription claims for enrolled beneficiaries and have been used previously to describe changes in medication utilization in their respective jurisdictions (18-20). While each of these three jurisdictions may provide access to subsidized medicines for a wide age range of people, we limited our analysis to beneficiaries ≥65 years of age, as older adults are the focus of the Choosing Wisely benzodiazepine recommendations (9-12). This study was based on a common protocol and analyses were harmonized across all three individual databases.

Study population

The study population consisted of all people 65 and older in each of the three jurisdictions from 1 January 2010 until 31 December 2016, apart from the U.S. where data was only available until 8 December 2016. The study denominator for each year included any individual that was alive for part of the year and had at least one prescription claim for any medicine. We restricted all analyses to people for whom we had complete capture of prescription claims across the study period; in the Australian cohort this meant restricting the population to people who were concession card holders for the entire period (18).

Medicines of interest

We identified benzodiazepine derivatives – as defined by the Anatomical Therapeutic Chemical (ATC) classification system (i.e., classes N03AE, N05BA, and N05CD) – subsidized within each jurisdiction. The specific benzodiazepines available within each jurisdiction varied (Supplementary Table S1); we excluded intravenous formulations.

Measures and statistical analysis

Characteristics of study populations

We report the sex and age group (65-74, 75-84, and ≥85 years) of all people ≥65 years with at least one prescription claim between 2010 and 2016 by jurisdiction. In addition we report these characteristics for people ≥65 years with at least one benzodiazepine claim over this study period.

Annual incidence and prevalence

We determined yearly incident and prevalent benzodiazepine use in each jurisdiction from 2010 to 2016 (Supplementary Figure S1). We estimated *incident (new) use* by identifying persons with a benzodiazepine prescription claim during a given calendar year and no prescription claims for a benzodiazepine during the previous 12 months. We estimated *prevalent use* by identifying persons with at least one prescription claim for a benzodiazepine within a given calendar year. We present incidence and prevalence in each jurisdiction overall and further stratified by age (65-74, 75-84, and ≥85 years) and sex. The denominator for each jurisdiction was the number of people within the corresponding age or sex category that had a prescription claim for any

medication during a given year. Incidence and prevalence were expressed as per 100-population.

To determine whether annual incidence and prevalence changed year on year in each jurisdiction, we used multiple Poisson regression to model the number of people with new or prevalent benzodiazepine use each year. Along with study year, we adjusted the model for age group, sex, and the log of the denominator (i.e., total number of people) as an offset term. We reported fixed effects as rate ratios with 95% confidence intervals. Due to significant over-dispersion, as assessed by the Lagrange multiplier test, a negative binomial distribution was used to produce more accurate parameter estimates.

All analyses were performed with SAS, version 9.3 (SAS Institute Inc.) and Stata version 12 (Statacorp).

Ethics and data access approval

The analyses for this study were approved by the: Institutional Review Board of the VA Ann Arbor Healthcare System; the Research Ethics Board at Sunnybrook Health Sciences Centre; and the New South Wales Population and Health Services Research Ethics Committee and Department of Human Services. The data remained within each jurisdiction.

RESULTS

There were differences in age and sex strata among all three study populations (Table 1). Of note there were more people in the older age groups (75-84 and

85+ years) in the Australian study population compared to the other jurisdictions. While the Australian and Ontarian study populations had similar proportions of men and women, the U.S. VA population was almost entirely male.

Annual incidence and prevalence

Our estimates of annual incidence and prevalence by jurisdiction are presented in Figure 1 (data available in Supplementary Table S2). We observed a significant linear decline in incident benzodiazepine use in the U.S, (2.6% in 2010 to 1.7% in 2016). The decline in incident benzodiazepine use in Ontario (from 6.0% in 2010 to 4.4% in 2016) was also significant over the entire study period but there was a greater decline between 2011 and 2012 compared to prior and subsequent years. We did not observe a statistically significant change in incident benzodiazepine use in Australia over the study period from (7.0% in 2010 to 6.7% in 2016). (Figure 1, Supplementary Table S3).

There was a significant decline in prevalent benzodiazepine use in all jurisdictions between 2010 and 2016, decreasing from 9.2% to 7.3% in the U.S, 18.2% to 13.4% in Ontario and 20.2% to 16.8% in Australia. The rate of this decline was relatively linear for all jurisdictions.

In general, age-stratified trends followed similar trajectories within jurisdictions (Figure 1b). For both Ontario and Australia, people aged 85 years or older had the highest prevalence followed by 75-84 year olds and then by 65-74 year olds (Figure 1c and 1d respectively). In the U.S, this pattern was reversed, with 65-74 year olds having the highest prevalence. Annual incidence was similar across age

groups for Ontario and Australia, while the 65-74 year olds consistently had the highest incident use in the U.S. VA data. Differences in incidence and prevalence between age groups within each jurisdiction were supported by our multiple regression analyses across all jurisdictions (Supplementary Table S3).

Women had the highest incident and prevalent benzodiazepine use across the study period in all three jurisdictions and trends for men and women followed similar trajectories (Supplementary Figure S2). This observation was supported in our multiple regression analyses, where female sex was significantly associated with increased rates of both incident and prevalent benzodiazepine prescriptions, irrespective of jurisdiction (Supplementary Table S3).

DISCUSSION

The U.S., Canada, and Australia were early adopters of the Choosing Wisely campaign (in 2012, 2014 and 2015 respectively) and all emphasize that benzodiazepines should not be prescribed to older persons. Hence we have used a standardized methodology to measure annual incident and prevalent benzodiazepine use between 2010 and 2016 in these jurisdictions. While using a standardized methodology facilitates comparisons of annual trends between jurisdictions, differences in underlying study populations make direct comparisons of absolute incidence and prevalence challenging. However, we found small but statistically significant decreases in benzodiazepine incidence and prevalence across all three jurisdictions, with the exception of incidence in Australia, which did to reach statistical significance. In addition, among older adults, incidence and prevalence were highest in those aged 85 and older in

Ontario and Australia, but decreased with advancing age in the U.S. VA population.

It is unclear whether the decrease in benzodiazepine use observed in the U.S. VA population in this study applies more broadly to the general U.S. population. Prevalence figures in this study are similar to those of the general U.S. population in 2008 based on a national prescription database covering around 60% of all retail pharmacy prescriptions (14). However, the decreasing use over time found here is in contrast to recent non-VA U.S. studies demonstrating stable or increasing in use. Analysis of the nationally-representative Medical Expenditure Panel Survey suggested an increase in the prevalence of benzodiazepine use among older adults between 1996 and 2013 (from 4.1% to 5.6% of older adults), although this increase appeared to plateau in the last three years of the study (21). A separate analysis of U.S. ambulatory clinic visits to primary care providers found an increase in visits in which benzodiazepines were prescribed to older adults between 2003 and 2012 (from 5.6% to 8.7% of visits) (22). While overall prevalence in the VA would be expected to be lower than the general population because the population is predominantly male, and fewer men are prescribed benzodiazepines (14), our observed trends persisted following stratification by sex. There have been a number of VA-specific policy and education initiatives focused on safe psychotropic prescribing as well as treatment guidelines (e.g., for PTSD) that may have all contributed to the observed reductions in benzodiazepine prescribing within the VA system (23). It is also conceivable that prescribing has declined more recently in the non-VA U.S. population, but this is yet to be demonstrated.

Our findings of decreasing benzodiazepine use in Australia and Ontario are consistent with previous studies in these jurisdictions (15, 24) and may also be the result of recent initiatives in each jurisdiction to address this practice (20, 25).

The decreases in benzodiazepine use in older adults generally described worldwide are likely to be in response to safety concerns and lack of evidence of effectiveness. Benzodiazepine related "Z-drugs" such as zopiclone and zolpidem were not measured in this study but there are concerns that they are being used in preference to conventional benzodiazepines, putatively because of perceptions of a superior safety profile and this warrants further investigation (26).

Despite the modest decreases in benzodiazepine incidence and prevalence seen in our study, the rates of benzodiazepine use in older adults remain high, in spite of consistent messaging about the hazards of using benzodiazepines in this population. Ongoing use may be related to provider's tendency to minimize the risks of prescribing to older adults (27), and even patients may do the same (28). Limited access to non-pharmacological alternatives such as psychotherapy (29) and limited physician time (14) are other factors associated with ongoing benzodiazepine initiation.

As demonstrated previously in the general U.S. population (14), as well as for Australia and Ontario in this study, benzodiazepine use typically increases with

age, so that rates are highest among the oldest individuals. This is particularly concerning as potential harms may be even greater among those aged 85 and older. It is unusual that in the U.S. VA population, the 65-74 year old age group have the highest rates of use. This may be related to aging of Vietnam-era veterans, who have more diagnosed depression and anxiety than earlier veteran cohorts.

In Ontario, there was a marked decline in incidence between 2011 and 2012. This may be a result of the implementation of the province's *Narcotics Safety and Awareness Act* (November 2011) and Narcotics Monitoring System program (May 2012), a two-pronged approach to limit potentially inappropriate benzodiazepine use (20). Similar real-time prescription drug monitoring programs are becoming increasingly prevalent in the U.S., in an effort to limit prescription drug abuse and potentially reduce overdose risk (30). Despite their benefits, prescription drug monitoring programs are unlikely to be nuanced enough to pinpoint potentially inappropriate use as opposed to abuse (5). Australia is yet to implement national prescription drug monitoring or other similar dedicated policy efforts, which might partially explain the lack of change in new use of benzodiazepines in the elderly. At a clinical level, limiting the conversion of new-use to chronic use may be the most effective initial step in reducing the prevalence of benzodiazepine use, as ceasing chronic use can be more challenging. This could be achieved by explicitly limiting the duration of new prescriptions and by not routinely providing repeat prescriptions. For people who have been using benzodiazepines for a long-time, a discussion

around the risks and benefits of continued therapy and attempts to gradually dose reduce might be the best strategy (31).

LIMITATIONS

Only subsidized medicines are captured within this study, meaning that the prevalence of benzodiazepine use may be underestimated if patients obtain prescriptions outside of the subsidising program. In Australia, unrecorded private prescribing accounts for up to 10% of all benzodiazepine prescriptions (32) and this may also be an issue for the Ontarian and U.S. VA programs. In addition, restricting the Australia study cohort to people who were continuous concession cardholders may limit the generalizability of the results, as this population tends to be older and have greater comorbidity than the general population. Similarly, while the U.S. study cohort is the largest population in this analysis, it is limited to older adults receiving care in the VA healthcare system. While it was not the intention of this study to identify 'true' new use (i.e. first ever use), it should be noted that the 12-month look back used to classify incident use might overestimate 'true' new use. We did not measure benzodiazepine related Z-drugs because these were not consistently subsidized across all jurisdictions. There were significant differences in the age and sex strata of the three populations and benzodiazepine sub-populations reflecting differences in organizational structures, though these were accounted for in our regression models of trends over time. Finally, other information such as treatment duration, clinical indication, and co-morbidity was not available consistently across all three jurisdictions, so it is not possible to compare and adjust for these differences between populations.

CONCLUSION

In this analysis across three countries, incident and prevalent benzodiazepine use amongst older adults has decreased in the VA system in the U.S. and Ontario, and prevalent use has decreased in Australia. Our findings are generally consistent with separate international studies that have used varying methods. However, use in the respective older adult populations remains high and warrants further attention from clinicians and policy makers. A detailed description of the methodology used to measure low-value prescribing practice, as well as a description of historical trends for this practice, facilitates harmonization of methodologies across countries and jurisdictions to allow other jurisdictions to benchmark this practice using the same methodology. This also paves the way for future internationally coordinated efforts to decrease low-value care by investigating the motivations for prescribing and the effectiveness of initiatives used to limit benzodiazepine use using gold standard methods such as interrupted time series analyses.

ACKNOWLEDGEMENTS

Conflict of Interest

None to declare

Author Contributions

JB performed Australian analyses, all regression analyses and drafted the manuscript. DM project managed U.S. data analysis and reviewed the manuscript. RVI performed U.S. data analysis. ZB project managed Ontarian data analysis and reviewed the manuscript. GM performed Ontarian data analysis. EK, SB and AE

assisted in drafting the manuscript using their jurisdictional perspectives. SP reviewed all drafts of the manuscript and took overall responsibility for the project direction.

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FIGURE LEGENDS

Figure 1: Incidence and prevalence of benzodiazepine dispensing a. in all jurisdictions, b. U.S. c. Ontario, and d. Australia.

*U.S. data available through 8 December 2016; incidence and prevalence calculated accordingly.

SUPPLEMENTARY MATERIAL

Supplementary Table S1: List of benzodiazepines available in each jurisdiction

Supplementary Figure S1: Flow chart outlining incidence and prevalence calculation

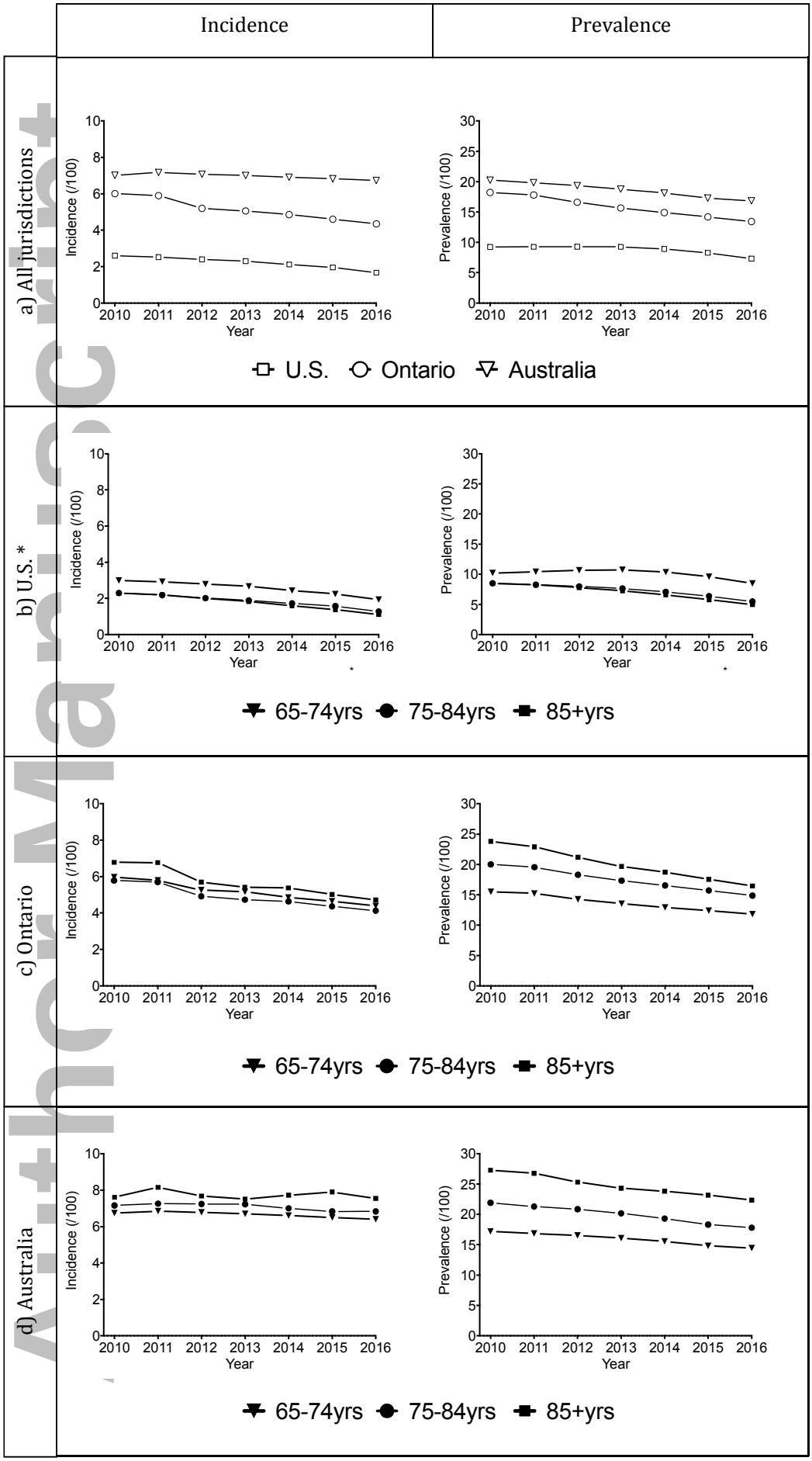
Supplementary Figure S1: Incidence and prevalence in each jurisdiction stratified by sex

Supplementary Table S2: Raw incidence and prevalence data in each jurisdiction

Supplementary Table S3: Results of multivariable negative binomial regression modelling

Table 1: Characteristics of the three study populations (2010-2016).

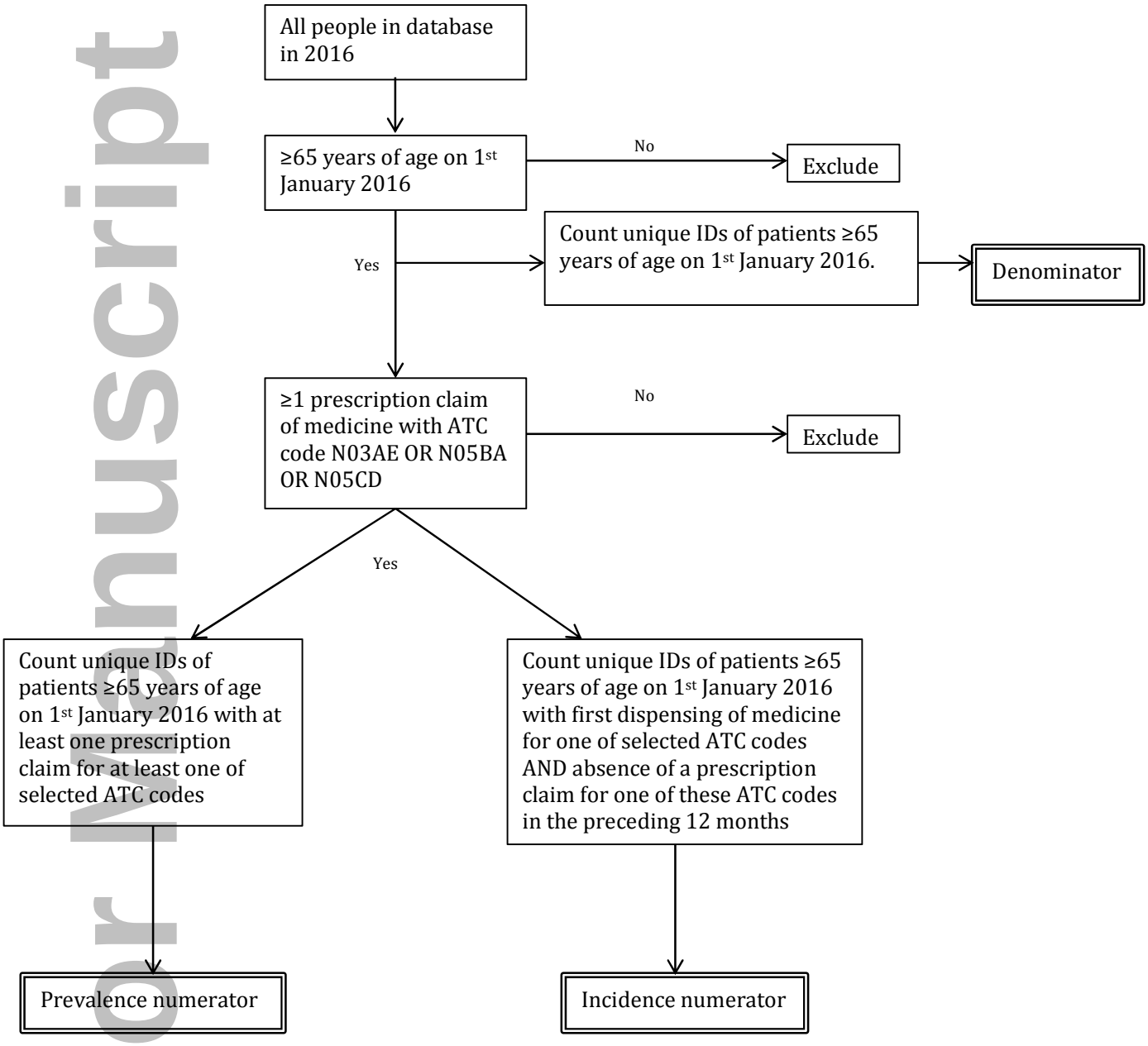
		U.S. (/1000 people)	Ontario (/1000 people)	Australia (/1000 people)
Study population, n		3888	2595	1787
Age, n (%)				
	65-74	2442 (62.8)	1736 (66.9)	888 (49.7)
	75-84	1049 (27.0)	626 (24.1)	646 (36.1)
	85+	398 (10.2)	234 (9.0)	254 (14.2)
Sex, n (%)				
	Female	78 (2.0)	1420 (54.7)	1010 (56.5)
	Male	3810 (98.0)	1175 (45.3)	777 (43.5)
≥1 benzodiazepine dispensed, n (%)		527 (13.6)	686 (26.4)	332 (18.6)
Age, n (%)				
	65-74	360 (68.3)	357 (52.0)	141 (42.5)
	75-84	125 (23.6)	221 (32.3)	128 (38.7)
	85+	43 (8.1)	108 (15.7)	62 (18.8)
Sex, n (%)				
	Female	14 (2.6)	439 (64.0)	221 (66.7)
	Male	513 (97.4)	247 (36.0)	111 (33.3)



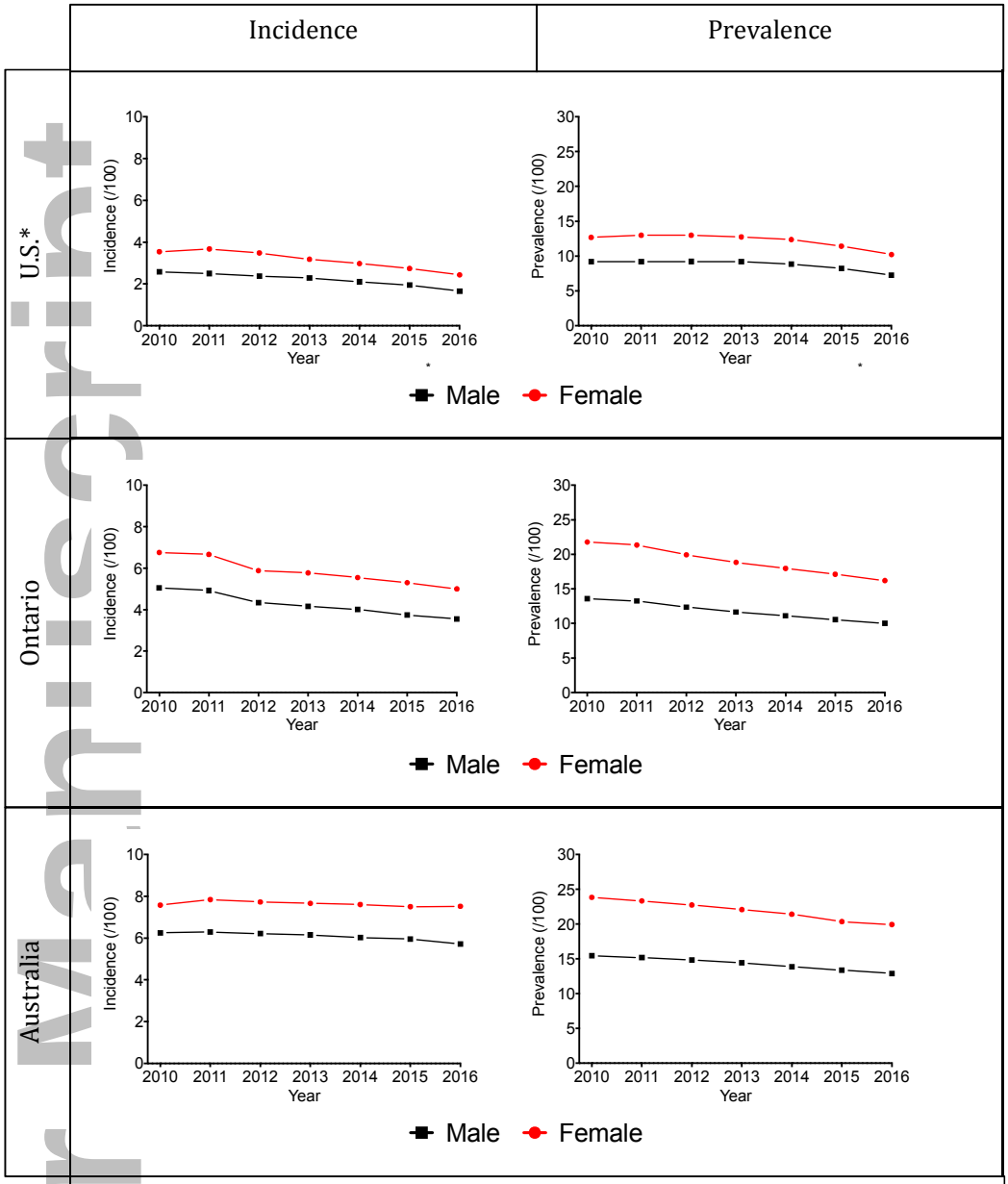
SUPPLEMENTARY

Supplementary Table S1: Benzodiazepines available within each jurisdiction.

Benzodiazepine	U.S.	Ontario	Australia
Alprazolam	✓	✓	✓
Bromazepam		✓	✓
Chlordiazepoxide	✓	✓	
Chlordiazepoxide/ Amitriptyline	✓		
Chlordiazepoxide/ Clidinium	✓		
Clobazam	✓		
Clonazepam	✓	✓	
Clorazepate	✓	✓	
Diazepam	✓	✓	✓
Estazolam	✓		
Flunitrazepam			✓
Flurazepam		✓	
Lorazepam	✓	✓	
Nitrazepam		✓	✓
Oxazepam	✓	✓	✓
Temazepam	✓	✓	✓
Triazolam	✓	✓	



Supplementary Figure S1: Flow chart detailing derivation of denominator and numerators for **prevalence and incidence** calculation using 2016 as an example.



Supplementary Figure S2: Incidence and prevalence of benzodiazepine dispensing in the U.S., Ontario and Australia by sex.

*Data available until 12/8/16, incidence and prevalence calculated accordingly.

Supplementary Table S2: Prevalence and incidence by age group and sex for each jurisdiction.

Year, Age Group and Sex	U.S.			Ontario			Australia		
	Total (n)	Prevalence (%)	Incidence (%)	Total (n)	Prevalence (%)	Incidence (%)	Total (n)	Prevalence (%)	Incidence (%)
2010									
Total	2015199	9.2	2.6	1654755	18.2	6	231770	20.2	7
65 to 74	874655	10.2	3	847717	15.5	6	115977	17.2	6.7
75 to 84	838806	8.5	2.3	583938	20	5.8	85586	21.9	7.2
85+	301738	8.5	2.3	223100	23.8	6.8	30207	27.3	7.6
Male	1977382	9.2	2.6	721069	13.6	5	99138	15.4	6.3
Female	37817	12.7	3.5	933686	21.8	6.8	132632	23.8	7.6
2011									
Total	1720610	9.4	2.6	1289996	16.4	5.8	181694	18.4	6.9
65 to 74	926839	10.4	2.9	873040	15.2	5.8	119439	16.9	6.8
75 to 84	790930	8.3	2.2	591835	19.6	5.7	88019	21.3	7.3
85+	319530	8.3	2.2	234963	22.9	6.8	32321	26.8	8.2
Male	1999524	9.2	2.5	744700	13.3	4.9	103203	15.2	6.3
Female	37775	13	3.7	955138	21.3	6.7	136576	23.3	7.8
2012									
Total	1068971	10.8	2.8	1770130	16.4	5.6	242403	18.9	7.2
65 to 74	1037973	10.7	2.8	916739	14.3	5.3	123195	16.5	6.8
75 to 84	744892	8	2	601861	18.3	4.9	90202	20.9	7.2
85+	329342	7.8	2	246067	21.2	5.7	34541	25.3	7.7
Male	2073511	9.2	2.4	777321	12.4	4.3	107226	14.8	6.2
Female	38696	13	3.5	987346	19.9	5.9	140712	22.7	7.7

013									
Total	1216458	10.8	2.7	1668962	16.3	5.2	228223	19.3	7.1
65 to 74	1198225	10.7	2.7	977954	13.6	5.2	126356	16.1	6.7
75 to 84	704833	7.7	1.9	613639	17.3	4.7	92063	20.2	7.2
85+	329845	7.3	1.8	257628	19.7	5.4	36382	24.3	7.5
Male	2192771	9.2	2.3	818982	11.7	4.2	110664	14.4	6.2
Female	40132	12.7	3.2	1030239	18.8	5.8	144137	22.1	7.7
014									
Total	2899906	9.4	2.2	1903354	13.1	4.5	243317	16	6.5
65 to 74	1354332	10.4	2.4	1026662	12.9	4.9	130255	15.6	6.6
75 to 84	679396	7.1	1.7	626741	16.5	4.6	94269	19.3	7
85+	323436	6.6	1.6	268085	18.7	5.4	38592	23.8	7.7
Male	2314717	8.8	2.1	855078	11.1	4	114905	13.9	6
Female	42447	12.3	3	1066410	18	5.5	148211	21.4	7.6
015									
Total	1500801	9.6	2.3	1424740	14	4.7	187381	16.7	6.7
65 to 74	1491150	9.6	2.3	1070625	12.4	4.6	134915	14.8	6.5
75 to 84	656867	6.4	1.6	638961	15.7	4.4	96498	18.3	6.8
85+	318450	5.8	1.4	277489	17.5	5	40326	23.2	7.9
Male	2420880	8.2	1.9	886911	10.5	3.7	119378	13.4	6
Female	45587	11.4	2.7	1100164	17.1	5.3	152361	20.4	7.5
016									
Total	1579050	8.5	1.9	1475091	13.3	4.4	191224	16.4	6.8
65 to 74	1569109	8.5	1.9	1114499	11.8	4.4	137404	14.5	6.4
75 to 84	628718	5.5	1.3	651879	14.9	4.1	98998	17.8	6.8
85+	318146	5	1.1	289058	16.5	4.7	41593	22.4	7.6

Male	2466729	7.3	1.7	920445	10	3.6	122482	12.9	5.7
Female	49244	10.2	2.4	1134991	16.2	5	155513	19.9	7.5

Supplementary Table S3: Multivariable negative binomial regression modeling where measure is outcome variable and factor is explanatory variable.

Jurisdiction*	Measure	Factor	RR	95% CI
U.S.	Prevalence	Year	0.94	0.93-0.95
		Age group (y)[a]		
		75-84	0.76	0.71-0.80
		85+	0.66	0.62-0.70
		Male[b]	0.72	0.69-0.75
	Incidence	Year	0.92	0.91-0.92
		Age group (y)[a]		
		75-84	0.75	0.71-0.79
		85+	0.69	0.66-0.73
		Male[b]	0.69	0.66-0.72
Ontario	Prevalence	Year	0.95	0.94-0.95
		Age group (y)[a]		
		75-84	1.26	1.23-1.30
		85+	1.42	1.39-1.46
		Male[b]	0.65	0.64-0.66
	Incidence	Year	0.94	0.93-0.95
		Age group (y)[a]		
		75-84	0.95	0.91-1.00
		85+	1.11	1.06-1.17
		Male[b]	0.77	0.74-0.80
Australia	Prevalence	Year	0.97	0.97-0.97
		Age group (y)[a]		
		75-84	1.26	1.24-1.28
		85+	1.51	1.48-1.54
		Male[b]	0.67	0.66-0.68
	Incidence	Year	0.99	0.98-1.00
		Age group (y)[a]		
		75-84	1.08	1.03-1.13
		85+	1.18	1.13-1.24
		Male[b]	0.83	0.80-0.87

Note: RR = rate ratio; CI = confidence interval.
*a negative binomial model was built for each jurisdiction via PROC GENMOD.
[a] [ref] = 65-74 y.
[b] [ref] = Female