HOSPITAL MEDICINE

Initiation of Benzodiazepines in the Elderly After Hospitalization

Chaim M. Bell, MD, PhD^{1,2,3,4}, Hadas D. Fischer, MD², Sudeep S. Gill, MD MSc^{2,5},
 Brandon Zagorski, MS², Kathy Sykora, MSc², Walter P. Wodchis, PhD^{2,4,6}, Nathan Herrmann, MD⁷,
 Susan E. Bronskill, PhD^{2,4}, Phil E. Lee, MD⁸, Geoff M. Anderson, MD, PhD^{2,4}, and Paula A. Rochon,
 MD, MPH^{2,3,4,9}

¹Department of Medicine, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, Canada M5B 1W8; ²Institute for Clinical Evaluative Sciences, Toronto, Canada; ³Department of Medicine, University of Toronto, Toronto, Canada; ⁴Department of Health Policy Management and Evaluation, University of Toronto, Toronto, Canada; ⁵Department of Medicine, Queen's University, Kingston, Canada; ⁶Toronto Rehabilitation Institute, Toronto, Canada; ⁷Department of Psychiatry, University of Toronto, Toronto, Canada; ⁸Department of Medicine, University of British Columbia, Vancouver, Canada; ⁹Kunin-Lunenfeld Applied Research Unit, Baycrest, Toronto, Canada.

OBJECTIVE: To estimate the rate of new chronic benzodiazepine use after hospitalization in older adults not previously prescribed with benzodiazepines.

DESIGN: Retrospective cohort study using linked, population-based administrative data.

SETTING: Ontario, Canada between April 1, 1992 and March 31, 2005.

PARTICIPANTS: Community-dwelling seniors who had not been prescribed benzodiazepine drugs in the year before hospitalization were selected from all 1.4 million Ontario residents aged 66 years and older.

MAIN OUTCOME MEASURES: New chronic benzodiazepine users, defined as initiation of benzodiazepines within 7 days after hospital discharge and an additional claim within 8 days to 6 months. We used multivariate logistic regression to examine for the effect of hospitalization on the primary outcome after adjusting for confounders.

RESULTS: There were 405,128 patient hospitalizations included in the cohort. Benzodiazepines were prescribed to 12,484 (3.1%) patients within 7 days of being discharged from hospital. A total of 6,136 (1.5%) patients were identified as new chronic benzodiazepine users. The rate of new chronic benzodiazepine users decreased over the study period from 1.8% in the first year to 1.2% in the final year ($P < .001$). Multivariate logistic regression found that women, patients admitted to the intensive care unit or nonsurgical wards, those with longer hospital stays, higher overall comorbidity, a prior diagnosis of alcoholism, and those prescribed more medications had significantly elevated adjusted odds ratios for new chronic benzodiazepine users. Older individuals had a lower risk for the primary outcome.

CONCLUSION: New benzodiazepine prescription after hospitalization occurs frequently in older adults and may result in chronic use. A systemic effort to address this risky practice should be considered.

KEY WORDS: benzodiazepine initiation; elderly; posthospitalization.

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INTRODUCTION

Benzodiazepines are commonly prescribed to older adults with sleep-related complaints.^{1–3} Their use has been linked to serious adverse events such as residual daytime sedation, cognitive impairment, fall-related injuries including hip fractures, and motor vehicle collisions, particularly when combined with other drugs or alcohol.^{4–8} An important but often overlooked issue is that long-term use of benzodiazepines can lead to dependence.^{9,10} Recognition of the consequences of chronic benzodiazepine use has even resulted in quality indicators for monitoring its prevalence.^{11–13} This has motivated efforts to wean many seniors off benzodiazepines.^{14,15} Abrupt discontinuation of benzodiazepines, however, can lead to significant withdrawal symptoms.^{9,10} Thus, a more effective approach may be the development of programs that aim to avoid their initial prescription, including ones that restrict reimbursement.¹⁶ Effective strategies to reduce unnecessary benzodiazepine initiation are needed.

Many patients are first introduced to benzodiazepines during hospitalization.^{17–23} Short-term insomnia and consequent benzodiazepine initiation may result from a number of factors associated with hospitalization such as the effects of illness and new medications, environmental factors including noise and disruption of usual sleeping schedules, and anxiety. Although the intent of the benzodiazepine prescription may have been to manage the short period of time that the patient is in hospital, there are concerns that its initiation in this setting may result in chronic use after discharge, together with its accompanying risks.²⁴

We sought to determine the rate of initiation of chronic benzodiazepine prescriptions after hospitalization in elderly patients not previously prescribed with benzodiazepines.

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METHODS

Overview

This retrospective cohort study used population-based administrative data covering all 1.4 million Ontario residents aged 66 years and older to select those community-dwelling seniors who had not been prescribed benzodiazepine drugs in the year before hospitalization. Individuals were then assessed whether benzodiazepines were initiated after hospital discharge and if there was a subsequent renewal of prescription.

Setting and Databases

We conducted a retrospective cohort study of multiple-linked health care databases in Ontario, Canada between April 1, 1992 and March 31, 2005. Data on individuals were linked using an encrypted unique identifier at the Institute for Clinical Evaluative Sciences (ICES). The Ontario Drug Benefit (ODB) database records data on all prescription medications dispensed to patients over the age of 65 years.^{25,26} The Canadian Institute for Health Information Discharge Abstract Database (DAD) contains information on all hospitalizations in Ontario. There is excellent agreement between administrative hospitalization data and chart audit.²⁵ The Ontario Health Insurance Plan (OHIP) physician-billing database records information on inpatient and outpatient physician services. The Registered Persons Database (RPDB) contains demographic and vital status information for each Ontario resident. There is little basic information on patients missing in these databases.^{25,26} As a result of the comprehensive nature of universal health insurance in Ontario, analyses can be considered population-based.

Patients and Exposures

Individuals aged 66 years and above who were discharged alive after acute care hospital admissions in Ontario between April 1, 1995 and September 30, 2004 (DAD) were included in the cohort. The index date was defined as the date of hospital discharge.

Inclusions and Exclusions

For inclusion in the cohort, patients were required to have remained alive for at least 30 days after hospital discharge (RPDB) and could not have had any prescriptions for benzodiazepines in the year before hospital admission (ODB). To attribute a benzodiazepine dispensation to the hospitalization, patients transferred between hospitals were excluded from the analysis. Also, those who had another hospitalization 1 year before or 6 months subsequent to the index date and those who had long-term care residency 3 months before or 6 months subsequent to the index date were excluded from the analysis (DAD and ODB). These criteria were applied to more confidently ascribe the long-term benzodiazepine prescription to a particular hospitalization and avoid confounding issues related to other prescribers. Patients with a consult from a psychiatrist during their hospital stay and palliative care patients were also excluded to avoid possible indications for benzodiazepine prescription (OHIP and DAD) (Appendix).

Eligible patients could be included more than once (sampling with replacement).

Outcome

The primary outcome was new *chronic benzodiazepine use* after hospital discharge (ODB). This was defined as initial prescription of benzodiazepines ([List of benzodiazepines included on ODB plan, which were included in the analysis](#)) within 7 days after the index date *and* an additional claim within 8 days to 6 months after the index date. Patients filling a benzodiazepine prescription within 7 days of the index date were considered to be *early benzodiazepine users*. Individuals filling a prescription 8–180 days after hospital discharge were considered to be *late benzodiazepine users*.

Confounders and Predictors

We controlled for confounding factors such as age and sex. We assessed for predictors that might influence chronic benzodiazepine initiation. Patient-level factors included comorbid disease burden (as measured by the Charlson index), a history of alcoholism in the prior 3 years, and the number of distinct drugs prescribed in the previous year (ODB) ([ICU and Alcoholism Coding](#)). Models also included the length of hospital stay, whether there was an intensive care unit (ICU) admission during the hospitalization, and if surgery was performed (DAD) ([ICU and Alcoholism Coding](#)).

Statistical Analysis

The primary analysis documented the proportion of patients with new chronic use of benzodiazepines after hospital discharge. We used multivariate logistic regression to examine for the effect of hospitalization on the primary outcome after adjusting for confounders. We included the year of hospitalization as a class variable to control for time trends in the data and generalized estimating equations to account for the clustering effect of prescribing practices within hospitals.²⁷ This adjustment had little effect on the variance estimates. Multicollinearity was investigated using tolerances and variance inflation factors. The effects of exposure on the risk of chronic benzodiazepine prescription were expressed as odds ratios (OR) and 95% confidence intervals (CI).

All reported *P* values are two-tailed. Analyses were performed with SAS software version 9.1 (Cary, NC, USA). The study was approved by the research ethics committee of the Sunnybrook and Women's College Health Sciences Centre. We used protocols of the ICES in Ontario to maintain the confidentiality of the data.

RESULTS

Over the study period, 405,128 patient hospitalizations were included in the cohort. The median age was 76 (interquartile range [IQR] 71–82) and 53% were female (Table 1). More than one tenth had surgery and approximately 1/12 were admitted to the ICU. The median hospital length of stay was 5 days (IQR 3–9). A median of 6 (IQR 3–10) unique drugs was prescribed to each patient in the previous year.

Table 1. Characteristics of Patients Prescribed with Benzodiazepines After Hospitalization

	Chronic benzodiazepine users (n=6,136)	Early benzodiazepine users (n=12,484)	Late benzodiazepine users (n=29,207)	No benzodiazepine users (n=369,573)	Total (n=405,128)
Median age (IQR)	76 (71–81)	76 (71–81)	76 (71–82)	76 (71–82)	76 (71–82)
Female, n (%)	3,632 (59%)	7,163 (57%)	17,422 (60%)	193,757 (52%)	214,710 (53%)
Charlson index, n (%)					
0	3,322 (54%)	7,009 (56%)	16,610 (57%)	225,325 (61%)	245,622 (61%)
1	1,626 (27%)	3,223 (26%)	7,357 (25%)	92,575 (25%)	101,529 (25%)
2	620 (10%)	1,228 (10%)	2,913 (10%)	32,607 (9%)	36,128 (9%)
3+	568 (9%)	1,024 (8%)	2,327 (8%)	19,066 (5%)	21,849 (5%)
ICU stay during admission, n (%)	787 (13%)	1,508 (12%)	2,965 (10%)	30,076 (8%)	33,762 (8%)
Surgery, n (%)	574 (9%)	1,179 (9%)	3,430 (12%)	38,948 (11%)	42,983 (11%)
Median length of stay (IQR)	8 (4–14)	7 (4–13)	6 (3–11)	5 (3–9)	5 (3–9)
Median number of unique drugs in previous year (IQR)	7 (4–11)	7 (4–10)	7 (4–11)	6 (3–10)	6 (3–10)

Total patients studied=[(early+late users)–chronic users]+no users

Chronic benzodiazepine users: prescription 0–7 days and 8–180 days posthospital discharge; early benzodiazepine users: prescription 0–7 days post hospital discharge; late benzodiazepine users: prescription 8–180 days post hospital discharge; no benzodiazepine users: no prescription within 180 days post hospital discharge

Benzodiazepine Prescription

There were 12,484 (3.1%) patients who were early benzodiazepine users (i.e., newly prescribed benzodiazepines within 7 days of their hospital discharge) and 29,207 (7.2%) who were late benzodiazepine users (i.e., newly prescribed benzodiazepines between 8 days and 6 months of their hospital discharge). This resulted in 6,136 (1.5%) patients who were chronic benzodiazepine users (i.e., had the primary outcome of newly prescribed benzodiazepines within 7 days and between 8 days and 6 months after their hospital discharge). For all patients receiving benzodiazepine prescriptions, the most common benzodiazepine prescribed was lorazepam (Table 2). Oxazepam was the second-most prescribed benzodiazepine. The rankings for choice of benzodiazepine were similar for prescriptions filled within 7 days of hospital discharge and prescriptions filled between 8 and 180 days of hospital discharge. In 88% (5,400/6,136) of patients with the primary

outcome, their second prescription was for the same benzodiazepine as the first.

Yearly Changes

Over the entire study period, the rate of new chronic benzodiazepine prescriptions decreased slightly. It went from a high of 1.8% in the first year of the study to 1.2% in the final year of the study (Cochran–Armitage trend test, $P<.001$). Early benzodiazepine use decreased from 3.5% in 1995 to 2.6% in 2004 and late benzodiazepine use decreased from 7.8% in 1995 to 6.3% in 2004.

Adjusted Analysis

Older individuals had a lower risk for the primary outcome (Table 3). Females had a higher risk for new chronic use of benzodiazepines (adjusted OR 1.3 and 95% CI 1.2–1.4). For patients with ICU admissions, the adjusted OR for new chronic use of benzodiazepines was 1.4 (95% CI 1.3–1.5). Those with nonsurgical admissions, longer hospital stays, higher comorbidity, a diagnosis of alcoholism in the previous 3 years, and those prescribed with more medications also had significantly elevated adjusted OR for new chronic use of benzodiazepines.

DISCUSSION

Our long-term, population-based study found that more than 1% of patients discharged from acute care hospitals became chronic benzodiazepine users. Women, those with ICU and nonsurgical admissions, longer hospital stays, higher comorbidity, a diagnosis of alcoholism, and those prescribed more total medications were more likely to receive chronic benzodi-

Table 2. Types of Benzodiazepines Prescribed for all Patients Receiving Prescriptions

Benzodiazepine name	Frequency prescribed 0–7 d (%)	Frequency prescribed 8–180 d (%)
Lorazepam	7,090 (57)	15,739 (54)
Oxazepam	3,170 (25)	6,080 (21)
Temazepam	812 (6.5)	2,391 (8.2)
Diazepam	331 (2.7)	1,083 (3.7)
Clonazepam	323 (2.6)	1,255 (4.3)
Alprazolam	224 (1.8)	1,005 (3.4)
Chlordiazepoxide	124 (1.0)	197 (0.7)
Flurazepam	123 (1.0)	341 (1.2)
Nitrazepam	118 (1.0)	413 (1.4)
Triazolam	107 (0.9)	340 (1.2)
Bromazepam	62 (0.5)	363 (1.2)

Table 3. Results of Multivariate Logistic Regression

Characteristic	Adjusted odds ratio	95% confidence interval
Women	1.3	(1.2–1.4)
Nonsurgical	1.4	(1.3–1.5)
ICU stay	1.4	(1.3–1.5)
Age (reference=85+)		
66–69	1.4	(1.2–1.5)
70–74	1.2	(1.1–1.3)
75–79	1.1	(1.1–1.2)
80–84	1.1	(1.0–1.2)
Length of hospital stay, days (reference=1–3)		
4–9 days	1.7	(1.6–1.8)
10+ days	3.1	(2.9–3.4)
Number of unique drugs prescribed in the preceding year (reference=1–7)		
8–14	1.2	(1.2–1.3)
15+	1.5	(1.4–1.6)
Prior alcoholism diagnosis	1.5	(1.4–1.7)
Charlson comorbidity index (reference=0)		
1	1.0	(1.0–1.1)
2	1.0	(0.9–1.1)
3+	1.4	(1.3–1.5)

Multivariate logistic regression adjustment for year of hospitalization

azepine prescriptions. Older individuals were less likely to receive chronic benzodiazepine prescriptions.

Strengths of our study include its extensive time span and its consideration of more than 400,000 hospitalizations for community-dwelling elders in the province of Ontario. The outcome of interest was designed specifically to link closely and temporally the discharge from hospital to the initial benzodiazepine prescription. Our strict definition of chronic drug use required an initial prescription to be linked to a subsequent one. Moreover, we excluded all patients who had subsequent hospitalization within the follow-up period to isolate the effect of the index hospitalization. Because our aim was to target weakly indicated reasons for benzodiazepine prescriptions, we excluded patients with possibly stronger indications such as previous benzodiazepine use. Similarly, we did not include palliative care patients or those who received psychiatry consultation during their hospitalization. Finally, our employed statistical methods controlled for the clustering effect of prescribing practices within individual hospitals and yearly changes over the study period.

Recent large-scale data in this area is lacking. Others have demonstrated related results with smaller sample sizes and narrower time frames.^{17,18} The larger studies address a different issue in that they establish the role of hospitalization as a risk factor for new benzodiazepine use, whereas we provide the incidence of this practice (which they could not). Stufken et al.¹⁸ studied the effect of hospitalization on 10,000 hospitalized patients in the Netherlands from 1998–2000. They found that initiation of benzodiazepines were higher in the hospitalized group compared to controls but did not present drug initiation rates. Their study population was far younger (only one third were >65 years) and they did not take precautions to include clinically indicated benzodiazepine prescriptions. Moreover, their methodology made it difficult to isolate the effect of the index hospitalization on the prescription of benzodiazepines. Grad et al.¹⁷ used a nested case

control study in the community-dwelling elderly to determine if recent hospital admission was associated with new outpatient benzodiazepine prescriptions. They assessed just more than 20,000 elders in Quebec, Canada in 1990 and found that those hospitalized had more than a threefold adjusted risk of receiving a benzodiazepine prescription. However, their methodology also precluded a determination of the drug initiation rates and their outcome required only one prescription of benzodiazepines after hospitalization. They also could not exclude clinically indicated benzodiazepine prescriptions. Smaller, single-center studies have found benzodiazepine initiation rates of 0–5.3%.^{19–23} Our comparatively lower rate may be because of our selection criteria, our focus on the elderly (we observed a lower adjusted risk for the outcome in older cohorts), our strict outcome definition, the exclusion of long-term care residents, and the population-based use of administrative data for our analysis.

What message do these results impart to clinicians? In one sense it is encouraging that the rate of new chronic benzodiazepine use is not far higher than 1% and has declined over the study period. However, one should consider that the risk could be cumulative with multiple hospitalizations and that we purposely studied a select population.²⁸ Some may consider it encouraging that we found oxazepam and lorazepam to be the most prescribed drugs. These choices are less likely to be involved in drug–drug interactions and may be less toxic compared to alternatives such as diazepam or alprazolam, which may also have active metabolites.²⁹ Yet, others note that shorter-acting benzodiazepines may be no safer than longer-acting drugs and that we should instead focus on the potential indications for benzodiazepine prescription compared to the observed excess risk of adverse events.^{7,30–32} For example, the risk of falls after a new benzodiazepine prescription appears to be primarily front-loaded and may further enhance the already increased risk of falls after hospital discharge.^{32,33} A strategy that targets the patient groups whom we observed were most likely to be dispensed a new benzodiazepine prescription after hospitalization (e.g., ICU patients or those prescribed with more medications) seems the most clinically prudent.

Our study has limitations that merit discussion. First, the reliability of the information sources should be considered in any analysis using administrative data. Our data have demonstrated good reliability and our techniques have been validated in previous studies of drugs in the elderly.^{1,25,26,34} Second, we excluded individuals living in long-term care institutions. The rate of benzodiazepine use in these cases may not be as easily attributable to the effect of hospitalization and may not be generalizable from our results. Third, the data may underestimate the true rate of new chronic benzodiazepine prescription because our outcome definition required both a prescription within 7 days of hospital discharge and another from 8 days to 6 months afterward. It is conceivable that benzodiazepine prescriptions 8 days or more after discharge could have been related to the hospitalization and resulted in subsequent use. Moreover, our data may have underestimated benzodiazepine prescription if we excluded patients who died from benzodiazepine-related adverse events within 30 days of hospital discharge. Fourth, we could not determine the clinical context for benzodiazepine prescription or its reason for initiation, although this can be difficult even when sought explicitly.^{19,24} However, we specifically excluded those in long-term and palliative care, as well as individuals

with previous benzodiazepine use or psychiatric consultation to reduce the possibility of clinical indications. Finally, the rate for new prescriptions may indeed be higher for patients younger than age 65 as we found older age individuals to have a lower risk. Our study limitations suggest a downward bias on the overall findings relative to other studies that is therefore unlikely to change substantively the overall results.

Our results must be taken in the proper context with respect to the overall care of older adults. The study's inherent assumption is that the posthospitalization prescription of benzodiazepines is connected to their in-hospital prescription. This link is critical if we are to consider intervention programs aimed at decreasing benzodiazepine prescriptions. Our data demonstrate that about half of patients dispensed benzodiazepines within the first week after hospital discharge fill another prescription in the next 6 months. Initiatives such as the development of electronic medical records and medication reconciliation programs, or models of care that facilitate communication and coordination between hospital and community-based physicians may help further reduce the risk of new chronic benzodiazepine prescription, particularly when targeted to the higher-risk patients identified by our study.^{35–38} Larger-scale administrative impediments to benzodiazepine use have also been successful but may not be specific to hospitalized patients or produce a sustained effect.^{16,39} In particular, they might reduce benzodiazepine prescription but may not reduce some of their associated adverse effects.⁴⁰ Further, effective alternatives to benzodiazepines that treat insomnia should be considered.⁴¹ Discussions about reasons for prescription and associated risks as with any new medication should occur with patients before benzodiazepine initiation. In any event, a concerted, multidisciplinary effort at all critical components of the benzodiazepine prescription cascade—in hospital, at discharge, and ambulatory care prescription renewal—is worthy of future research.

Benzodiazepine use in the elderly is a practice that may best be addressed by preventing its initiation. Our study highlights that hospitalization may contribute to initial subsequent chronic use of benzodiazepines. Patient safety efforts should focus on this counterproductive practice so that hospitalization can be an opportunity for patients to heal and improve their health without contributing to additional adverse event risks.

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Corresponding Author: Chaim M. Bell, MD, PhD Department of Medicine, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, Canada M5B 1W8 (e-mail: bellc@smh.toronto.on.ca).

APPENDIX

Exclusion Codes

1. Psychiatry consult during the hospital stay (as described by one of the variables mdserv#1–8=64 before 2002 or prvserv1–8=00064 from 2002)
2. Exclude all subjects in palliative care (OHIP fee code A945, C945, C882, or C982, W872, W882, W972, or W982 or CIHI record with patserv=58).
3. Long-term care residents were identified by an LTC flag in the ODB Database.

LIST OF BENZODIAZEPINES INCLUDED ON ODB PLAN, WHICH WERE INCLUDED IN THE ANALYSIS

Benzodiazepines Included in the Analysis	
Shorter acting	Longer acting
Alprazolam	Chlordiazepoxide
Bromazepam	Clonazepam
Lorazepam	Diazepam
Oxazepam	Flurazepam
Temazepam	Nitrazepam
Triazolam	

ICU and Alcoholism Coding

1. ICU stay during index hospitalization (i.e., between admission and discharge dates, inclusive.). ICU stay was identified using OHIP ICU codes⁴²:
 - Comprehensive care–intensive care area (covers all aspects of ICU care including mechanical ventilation): G557-day 1 only, G558-day 2–10 inclusive, G559-day 11 onward.
 - Critical care–intensive care area (covers all aspects of ICU excluding mechanical ventilation): G400-day 1 only, G401-days 2–10 inclusive, G402-Days 11 onward.

Ventilatory support–intensive care area (covers management of mechanical ventilation only): G405-day 1 only, G406-days 2–10 inclusive, G407-days 11 onward.

1. Alcoholism based on *any* (not only primary diagnosis) admission diagnosis within the past 3 years (including index hospitalization) (for ICD-9-any CIHI dxcode: V113, 2911, 2913–2919, 3030, 3050, 3575, 4255, 5353, 5710–5713, 7903, 9808, 9809. For ICD-10-F100-F109, G621, I426, K292, K700–K704, K709, R780, T518, T519, Y910–Y913, Y919, Z811) or OHIP visit within past 3 years (OHIP dxcode: 291, 303).

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