Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD

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ABSTRACT Our purpose was to evaluate the association of new benzodiazepine use relative to non-use with adverse clinical respiratory outcomes among older adults with chronic obstructive pulmonary disease (COPD).

This was a retrospective population-based cohort study of Ontario, Canada, residents between 2003 and 2010. A validated algorithm was applied to health administrative data to identify adults aged 66 years and older with COPD. Relative risks (RRs) of several clinically important respiratory outcomes were examined within 30 days of incident benzodiazepine use compared with non-use, applying propensity score matching.

New benzodiazepine users were at significantly higher risk for outpatient respiratory exacerbations (RR 1.45, 95% CI 1.36–1.54) and emergency room visits for COPD or pneumonia (RR 1.92, 95% CI 1.69–2.18) compared to non-users. Risk of hospitalisation for COPD or pneumonia was also increased in benzodiazepine users, but was nonsignificant (RR 1.09, 95% CI 1.00–1.20). There were no significant differences in intensive care unit admissions between the two groups and all-cause mortality was slightly lower among new *versus* non-users.

Benzodiazepines were associated with increased risk for several serious adverse respiratory outcomes among older adults with COPD. The findings suggest that decisions to use benzodiazepines in older patients with COPD need to consider potential adverse respiratory outcomes.

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For editorial comments see page 284.

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Introduction

Benzodiazepine use is high among older adults with chronic obstructive pulmonary disease (COPD) [1, 2]. A recent population-based cohort study conducted in Ontario, Canada, found that new benzodiazepine use occurred in about one-third of older adults with COPD [2]. Patients with COPD may receive benzodiazepines for several reasons, including treatment for insomnia, depression and anxiety, and refractory dyspnoea, all of which are common problems in COPD [3–5].

Benzodiazepines have been linked with a variety of adverse respiratory physiology outcomes in COPD, including decreased minute ventilation [6–8], hypoxaemia and/or hypercapnea [6–11], dulling of central respiratory drive and chemoreceptor responsiveness to hypercapnea [8, 11, 12], decreased respiratory muscle strength [7], and ventilation–perfusion mismatch [6]. Based on this evidence, joint American Thoracic Society/European Respiratory Society guidelines recommend that hypnotics, such as benzodiazepines, be avoided in patients with severe COPD [13]. These potential adverse respiratory effects of benzodiazepines in COPD may also be accentuated in older adults given their altered pharmacokinetics that increase benzodiazepine half-life [14, 15]. Studies reporting on adverse physiological respiratory outcomes of benzodiazepines in COPD generally involved small numbers of subjects, individuals with more severe degrees of airflow obstruction, administration of a single benzodiazepine dose, and limited follow-up. Population-level studies that examine clinically important respiratory outcomes of real-world benzodiazepine use in a broader COPD population are lacking. We evaluated the association of new benzodiazepine use with the risk of adverse respiratory outcomes among older adults with COPD.

Methods

Study design

A population-based retrospective cohort design was used with data from April 1, 2003 to January 31, 2010. We used Ontario provincial health administrative databases to examine differences in the risk of adverse respiratory outcomes among new users and non-users of benzodiazepines among an established cohort of individuals with COPD. The province of Ontario has a multicultural population of about 13.5 million, which constitutes close to 40% of Canada's total population. Due to universal health insurance in Canada, analyses can be considered population-based. The study analysis was conducted at the Institute for Clinical Evaluative Sciences (ICES), Toronto, ON, Canada, and was approved by the research ethics board at Sunnybrook Health Sciences Centre, Toronto.

Data sources

Eight large Ontario provincial health care administrative databases were linked at an individual patient level for this study. The datasets are held securely in a de-identified form and analysed at the ICES. An established specific validated algorithm was used to identify Ontario adults with physician-diagnosed COPD (specificity 95.4%, 95% CI 92.6–97.4%; sensitivity 57.5%, 95% CI 47.9%–66.8%) [16]. This definition for COPD was based on three or more ambulatory claims for COPD within 2 years, or one or more hospitalisation for COPD [16]. Medication records were obtained from the Ontario Drug Benefit (ODB) claims database, which contains information on all publicly funded outpatient medications dispensed to Ontarians aged 65 years and older, including type of drug dispensed, days supplied, and whether the recipient was a resident of a long-term care home at the time of prescription dispensation. The coding accuracy and completeness of drug claims in the ODB are excellent, with an error rate of only 0.7% [17]. The Ontario Health Insurance Plan (OHIP) claims database (which contains information on patient contact with physicians in both ambulatory and hospital settings), the Canadian Institute for Health Information Discharge Abstract database (CIHI-DAD) (which contains information on hospitalisations), the Ontario Mental Health Reporting System (which contains information on all admissions to designated psychiatric beds), the National Ambulatory Care Reporting System database (which contains information on emergency room visits), and the Same-Day Surgery database (which contains information on surgical procedures not requiring overnight hospital stays) were used to identify adverse respiratory outcomes and/or comorbidities. Demographic and mortality data were obtained from the Registered Persons Database.

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Study population

In order to be considered for study inclusion, individuals first had to be Ontario residents, have validated physician-diagnosed COPD, and be 66 years of age or older, all between April 1, 2003 and December 31, 2009. Individuals with COPD younger than 66 years of age were excluded since information on incident medication receipt was not available for such persons in the ODB database. Although individuals with COPD younger than 66 years old were not included, COPD is a disease of older adults, with the vast majority of affected individuals being older than age 65 years [18]. Individuals receiving palliative care (based on physician service codes in OHIP and CIHI-DAD databases) in the year prior to index were excluded, since benzodiazepine use may differ in such a setting. We examined community-dwelling older adults and those living in long-term care facilities separately (see online supplement 1 for the long-term care cohort analysis).

Exposure to benzodiazepines

Exposed

All oral benzodiazepines covered under the ODB programme were considered (alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, nitrazepam, oxazepam, temazepam and triazolam). Benzodiazepine users were defined by incident use of any oral benzodiazepine listed above between April 1, 2003 and December 31, 2009. Incident use was defined as a drug dispensing following no receipt of any of the benzodiazepines listed above in the year prior to the incident date. Incident use was only counted once per individual and if an individual met criteria for incident use more than once during the observation window then only the first dispensation was considered. Individuals with incident benzodiazepine use at least once between April 1, 2003 and December 31, 2009 were excluded from entering the unexposed comparison group at any time. We studied incident benzodiazepine use, rather than prevalent use, because our purpose was to examine acute-onset adverse respiratory effects of benzodiazepines. The index date was the date the incident benzodiazepine was dispensed. Incident benzodiazepine receipt occurring prior to COPD diagnosis, prior to age 66 years, and prior to the start of our observation period of April 1, 2003 was not considered.

Unexposed

Non-users were not dispensed any benzodiazepines between April 1, 2003 and December 31, 2009. Cohort entry for non-users was defined as the most recent claim for any non-benzodiazepine medication on or before a date randomly chosen from the observation period. If the most recent claim took place more than 6 months before that date, or if it took place before the start of the 2003–2009 period, then the individual was excluded from the analysis. This method to define ''non-medication users'' has been used previously [19]. The index date was the date of the most recent non-benzodiazepine medication claim.

Propensity score matching

Given known significant differences in benzodiazepine exposure risk in this population [2], we used 1:1 propensity score matching without replacement to create matched samples of exposed and unexposed individuals [20]. We computed a propensity score for new benzodiazepine receipt by developing a logistic regression model with 26 covariates describing patient demographic and health characteristics that are known to be associated with benzodiazepine receipt in older adults with COPD [2] and that were felt to affect the outcomes of interest (table 1). Markers of COPD severity, healthcare utilisation, and general health status were included in the propensity score. See online supplement 2 for more details on our propensity score matching methods.

Study outcomes

Adverse respiratory outcomes that were examined within 30 days following the index date included: outpatient respiratory exacerbations (defined similar to others [22, 23] as receipt of an oral corticosteroid or respiratory antibiotic within plus or minus 7 days of a physician clinic/office visit for COPD or pneumonia and with the corticosteroid or antibiotic prescription having a supply date of 5–21 days); emergency room visits for COPD or pneumonia; hospitalisations for COPD or pneumonia; intensive care unit (ICU) admission during a hospitalisation for COPD or pneumonia; and all-cause mortality. Emergency room visits and hospitalisations for COPD or pneumonia were identified as outcomes if the diagnosis for the emergency room visit or hospitalisation was COPD or pneumonia, using ICD-10 codes (COPD: J41, J42, J43, J44; pneumonia: J09–18, J20–22, J40). We chose a 30-day follow-up period since we expected adverse events related to benzodiazepine use to occur relatively soon following their initiation. Furthermore, the median duration of benzodiazepine use among older adults with COPD has previously been found to be 30 days [2].

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TABLE 1 Baseline demographic and health characteristics of the community-dwelling cohort before and after propensity score matching

Baseline characteristics	Before matching			After matching		
	New benzodiazepine user	Non-benzodiazepine user	Standardised difference#	New benzodiazepine user	Non-benzodiazepine user	Standardised difference#
Subjects n	50 358	126 997		48 915	48 915	
Age years	76.7±6.8	76.6±7.3	0.02	76.71±6.81	76.77±7.23	0.01
Females	25 354 (50.3)	53 668 (42.3)	0.16	24 321 (49.7)	24 222 (49.5)	0.00
Low income based on ODB flag 1 year prior to index date	14 839 (29.5)	33 192 (26.1)	0.08	14 264 (29.2)	14 108 (28.8)	0.01
Income quintile						
1 (lowest)	12 433 (24.7)	30 056 (23.7)	0.02	12 000 (24.5)	12 018 (24.6)	0.00
2	11 305 (22.4)	28 711 (22.6)	0.00	10 981 (22.4)	10 964 (22.4)	0.00
3	9814 (19.5)	24 559 (19.3)	0.00	9556 (19.5)	9497 (19.4)	0.00
4	8809 (17.5)	22 559 (17.8)	0.01	8566 (17.5)	8579 (17.5)	0.00
5 (highest)	7846 (15.6)	20 653 (16.3)	0.02	7663 (15.7)	7709 (15.8)	0.00
Missing data	151 (0.3)	459 (0.4)	0.01	149 (0.3)	148 (0.3)	0.00
Rural setting	8705 (17.3)	22 421 (17.7)	0.01	8448 (17.3)	8531 (17.4)	0.00
Charlson score						
0	11 910 (23.7)	32 204 (25.4)	0.04	11 709 (23.9)	11 631 (23.8)	0.00
1	10 117 (20.1)	23 961 (18.9)	0.03	9801 (20.0)	9688 (19.8)	0.01
2	7706 (15.3)	18 222 (14.3)	0.03	7437 (15.2)	7490 (15.3)	0.003
⩾3	14 122 (28.0)	30 657 (24.1)	0.09	13 515 (27.6)	13 688 (28.0)	0.01
Missing data	6503 (12.9)	21 953 (17.3)	0.12	6453 (13.2)	6418 (13.1)	0.00
Duration of COPD prior to index date						
<2 years	12 851 (25.5)	44 263 (34.9)	0.20	12 723 (26.0)	12 708 (26.0)	0.00
2–5 years	10 730 (21.3)	25 494 (20.1)	0.03	10 435 (21.3)	10 416 (21.3)	0.00
>5 years	26 777 (53.2)	57 240 (45.1)	0.16	25 757 (52.7)	25 791 (52.7)	0.00
COPD exacerbation history 1 year prior to index date						
No exacerbations	28 260 (56.1)	79 591 (62.7)	0.13	27 850 (56.9)	27 850 (56.9)	0.00
⩾1 exacerbations not requiring presentation to hospital or ER	9972 (19.8)	22 827 (18.0)	0.05	9698 (19.8)	9698 (19.8)	0.00
⩾1 ER or hospital presentation	12 126 (24.1)	24 579 (19.4)	0.12	11 367 (23.2)	11 367 (23.2)	0.00
COPD exacerbation 30 days prior to index date	6419 (12.7)	9023 (7.1)	0.20	5686 (11.6)	5614 (11.5)	0.00
Previous ICU admission past 12 months	5850 (11.6)	9550 (7.5)	0.15	5336 (10.9)	5374 (11.0)	0.00
Total number of non-benzodiazepine drugs received in the past 1 year	12.2±6.3	10.4±5.7	0.31	12.00±6.11	11.98±6.18	0.00
Medications in past 180 days						
Short/long-acting β-agonists	18 173 (36.1)	42 184 (33.2)	0.06	17 420 (35.6)	17 317 (35.4)	0.00
Short/long-acting anticholinergics	16 268 (32.3)	43 099 (33.9)	0.03	15 711 (32.1)	15 677 (32.0)	0.00
Inhaled corticosteroids	11 340 (22.5)	24 435 (19.2)	0.08	10 872 (22.2)	10 882 (22.2)	0.00
Combination inhaled corticosteroid–long-acting β-agonists	12 313 (24.5)	31 241 (24.6)	0.00	11 809 (24.1)	11 782 (24.1)	0.00
Oral corticosteroids	8214 (16.3)	15 333 (12.1)	0.13	7651 (15.6)	7639 (15.6)	0.00
Theophylline	1754 (3.5)	3686 (2.9)	0.03	1683 (3.4)	1672 (3.4)	0.00
Respiratory antibiotics	22 808 (45.3)	47 177 (37.1)	0.17	21 703 (44.4)	21 718 (44.4)	0.00
Non-psychotic psychiatric disease	28 749 (57.1)	53 196 (41.9)	0.31	27 455 (56.1)	27 535 (56.3)	0.00
Alcoholism	2415 (4.8)	4918 (3.9)	0.05	2306 (4.7)	2283 (4.7)	0.00
Dementia	5958 (11.8)	13 600 (10.7)	0.04	5783 (11.8)	5890 (12.0)	0.00
Sleep disorder	28 789 (57.2)	63 817 (50.3)	0.14	27 639 (56.5)	27 711 (56.7)	0.00
Ischaemic heart disease	27 695 (55.0)	60 704 (47.8)	0.14	26 612 (54.4)	26 781 (54.8)	0.01
Congestive heart failure	15 928 (31.6)	36 354 (28.6)	0.07	15 329 (31.3)	15 499 (31.7)	0.01
Year of cohort entry						
2003	7378 (14.7)	16 438 (12.9)	0.05	7236 (14.8)	7351 (15.0)	0.01
2004	9144 (18.2)	14 979 (11.8)	0.19	8636 (17.7)	8702 (17.8)	0.00
2005	8112 (16.1)	13 577 (10.7)	0.17	7705 (15.8)	7651 (15.6)	0.00
2006	7173 (14.2)	14 166 (11.2)	0.10	6923 (14.2)	6908 (14.1)	0.00
2007	6573 (13.1)	15 860 (12.5)	0.02	6482 (13.3)	6400 (13.1)	0.01
2008	6143 (12.2)	19 845 (15.6)	0.10	6103 (12.5)	6087 (12.4)	0.00
2009	5835 (11.6)	32 132 (25.3)	0.34	5830 (11.9)	5816 (11.9)	0.00
Cohort entry in flu season	19 969 (39.7)	48 531 (38.2)	0.03	19 287 (39.4)	19 149 (39.1)	0.01

Data are presented as mean±SD or n (%), unless otherwise stated. ODB: Ontario Drug Benefit claims database; COPD: chronic obstructive pulmonary disease; ER: emergency room; ICU: intensive care unit. #: a standardised difference (*i.e.* the difference in the means or proportions divided by the standard deviation) of >0.10 is thought to indicate a potentially meaningful difference [21].

Sensitivity analyses

We performed two sensitivity analyses. First, we examined adverse respiratory outcomes stratifying by COPD exacerbation history in the year prior to the index date (*i.e.* no exacerbations *versus* one or more outpatient exacerbations with no exacerbations requiring presentation to hospital *versus* one or more exacerbations requiring presentation to hospital). COPD exacerbation history, a marker of COPD severity, is a potential confounder since it is associated both with the exposure (*i.e.* benzodiazepine receipt) [2] and the outcome (*i.e.* future COPD exacerbation risk) [23]. We examined our outcomes in the subgroup of individuals with less severe disease (*i.e.* no exacerbations in the year prior to index) as one way of overcoming confounding by indication. The merits of this method have been described in the literature [24, 25]. Secondly, adverse respiratory outcomes were examined by stratifying by the half-life of the benzodiazepine received and by examining the most commonly dispensed benzodiazepine (see online supplement 3 for these analyses).

Statistical analysis

New users of benzodiazepines in a given setting (living in the community *versus* in long-term care residence) were matched to non-users in the same setting at index on COPD exacerbation history in the year prior to index (to facilitate our planned subgroup analysis by this variable) and the propensity score (using methods described above). Descriptive statistics including standardised differences were calculated to compare the exposed and unexposed groups on all covariates before and after propensity score matching [21]. The absolute risk (AR) and relative risk (RR) with associated 95% confidence intervals for each outcome were estimated for the propensity score matched sample using previously described methods [26, 27]. The unexposed group was used as the reference in all analyses. Numbers needed to harm (NNH) with associated 95% confidence intervals were determined by calculating the inverse of the absolute risk [28]. In order to provide readers with information relating to the incidence of adverse respiratory outcomes over time that were significantly increased among new *versus* non-benzodiazepine users, we produced cumulative incidence function curves that accounted for the competing risk of death. All statistical analyses were conducted using SAS 9.3 statistical software (SAS Institute Inc., Cary, NC, USA). We used two-sided tests of significance at the $p<0.05$ level.

Results

A total of 177 355 community-dwelling individuals with COPD who were aged 66 years and older were identified between April 1, 2003 and December 31, 2009 (fig. 1). Of these, 50 358 (28.4%) were new benzodiazepine users. After propensity score matching, 48 915 community-dwelling individuals who were new benzodiazepine users were matched to an equivalent number of non-benzodiazepine users. No propensity score match was found for 1443 (2.9%) community-dwelling new users of benzodiazepines. Baseline demographic and health characteristics of this propensity score matched community-dwelling sample are described in table 1. New and non-benzodiazepine users were well-matched on all baseline characteristics, with standardised differences below 10% for all variables.

Compared to non-users, new users of benzodiazepines living in the community were at significantly higher risk for outpatient respiratory exacerbations (n=2381; AR 1.51%; RR 1.45, 95% CI 1.36–1.54) and emergency room visits for COPD or pneumonia (n=694; AR 0.68%; RR 1.92, 95% CI 1.69–2.18) (table 2). The NNH for these outcomes were 66 (95% CI 57–79) for outpatient respiratory exacerbations and 147 (95% CI 123–181) for emergency room visits for COPD or pneumonia. Although not significant, risk of hospitalisations for COPD or pneumonia was also elevated in new *versus* non-benzodiazepine users (n=943; AR 0.17%; RR 1.09, 95% CI 1.00–1.20). No significant difference between new and non-users of benzodiazepines was observed with respect to ICU admissions during hospitalisations for COPD or pneumonia. All-cause mortality was slightly lower among new benzodiazepine users (n=1398; AR -0.27%; RR 0.91, 95% CI 0.85–0.98). The cumulative incidence of outpatient respiratory exacerbations (fig. 2) and emergency room visits for COPD or pneumonia (fig. 3) across the 30-day observation period tended to be higher for new benzodiazepine users *versus* non-users, from about 5 days onwards.

In the community-dwelling cohort, in the subgroup of individuals with no exacerbations in the year prior to index, new users of benzodiazepines had significantly higher risk for outpatient respiratory exacerbations (n=659; AR 0.92%; RR 1.63, 95% CI 1.44–1.84), emergency room visits for COPD or pneumonia (n=199; AR 0.42%; RR 2.46, 95% CI 1.90–3.18), hospitalisations for COPD or pneumonia (n=244; AR 0.20%; RR 1.29, 95% CI 1.07–1.56) and all-cause mortality (n=624; AR 0.36%; RR 1.19, 95% CI 1.06–1.34) (table 3). There was no significant difference between new and non-users of benzodiazepines in this subgroup with respect to ICU admissions during hospitalisations for COPD or pneumonia. Significantly increased risk of outpatient respiratory exacerbations, as well as emergency room visits for COPD or pneumonia, were also found among new users in the subgroup of individuals with one or more outpatient exacerbations in the

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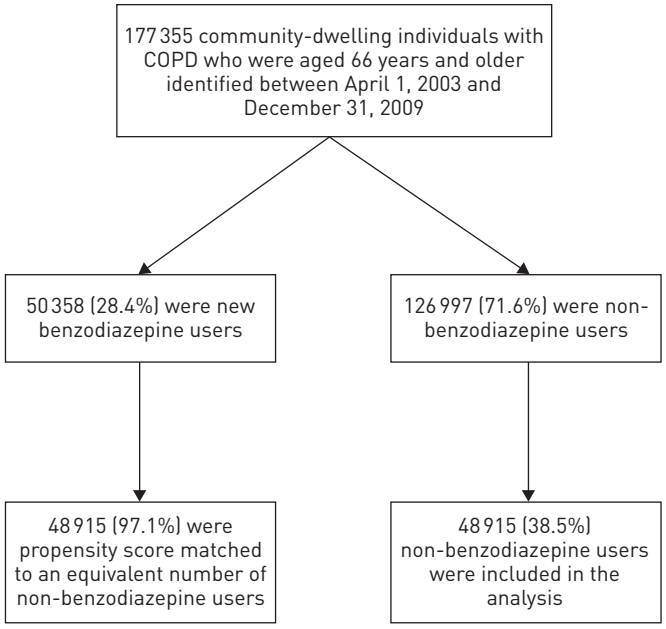

FIGURE 1 Flow diagram outlining exposed group identification process in the community-dwelling cohort. COPD: chronic obstructive pulmonary disease.

year prior to index and in the subgroup of individuals with one or more exacerbations requiring presentation to hospital in the year prior to index. In the subgroup of individuals with one or more exacerbations requiring presentation to hospital in the year prior to index, a significantly decreased risk of all-cause mortality was observed among new benzodiazepine users.

Discussion

Our population-based, propensity-matched cohort of 97 830 community-dwelling individuals with COPD showed that new users of benzodiazepines were at significantly higher risk for outpatient respiratory exacerbations as well as emergency room visits for COPD or pneumonia. These respiratory outcomes were consistently found among new benzodiazepine users across subgroups of differing COPD severity. To our knowledge, we are among the first to report that new use of benzodiazepines in older adults with COPD is associated with these important adverse patient outcomes.

Our results are consistent with previous studies that have reported links with benzodiazepines and a variety of adverse respiratory physiology outcomes in COPD [6–12]. Benzodiazepines are also reported to decrease arousability in healthy individuals during sleep [29], which may prolong the duration of respiratory physiological abnormalities or contribute to aspiration. Studies reporting adverse physiological respiratory outcomes of benzodiazepines in COPD generally included small numbers, individuals with more severe degrees of airflow obstruction, administration of a single benzodiazepine dose, and short follow-up periods

TABLE 2 Risk ratios (RR) for adverse respiratory outcomes for the matched community-dwelling cohort

Outcomes	Benzodiazepine use status	n (%)	RR (95% CI)
Outpatient respiratory exacerbation	New users	2381 (4.87)	1.45 (1.36–1.54)
	Non-users	1643 (3.36)	
ER visit for COPD or pneumonia	New users	694 (1.42)	1.92 (1.69–2.18)
	Non-users	361 (0.74)	
Hospitalisation for COPD or pneumonia	New users	943 (1.93)	1.09 (1.00–1.20)
	Non-users	863 (1.76)	
ICU admission during hospitalisation for COPD or pneumonia	New users	133 (0.27)	0.85 (0.68–1.07)
	Non-users	156 (0.32)	
All-cause mortality	New users	1398 (2.86)	0.91 (0.85–0.98)
	Non-users	1533 (3.13)	

ER: emergency room; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit.

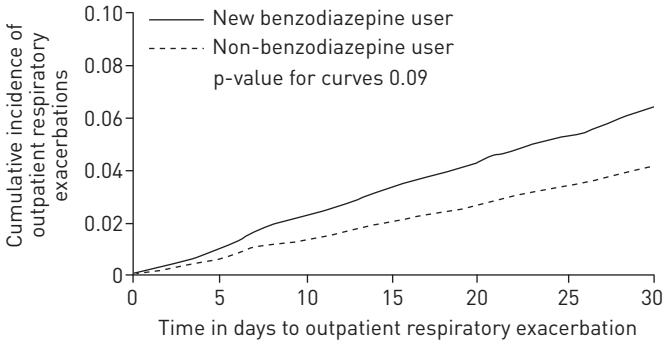

FIGURE 2 Cumulative incidence function curves for outpatient respiratory exacerbations among new and non-benzodiazepine users in the community-dwelling cohort.

(*i.e.* hours to a few days). In contrast, our study included a large population-based sample, individuals with a wide spectrum of COPD severity, real-world benzodiazepine doses and durations, longer follow-up periods, and important clinical outcomes.

While we found significantly increased relative risks of important respiratory outcomes among community-dwelling new benzodiazepine users, the absolute risks for these events were relatively small. However, given the high prevalence of COPD in Ontario (estimated to be as high as about 10% in the Ontario population of 13.5 million [18]), even these small absolute risks may be clinically important at the population level. No significant associations were identified in certain outcomes in the overall cohort (*i.e.* hospitalisations for COPD or pneumonia, ICU admissions during hospitalisations for COPD or pneumonia). However, some of these outcomes were based on relatively small numbers (*e.g.* the ICU admission outcome) and, unlike the outpatient exacerbation and emergency room visit outcomes, which are more patient-driven outcomes, hospitalisation and ICU admission can involve other non-patient-related factors (*e.g.* hospital bed availability and physician discretion) that we were unable to adjust for. Hospitalisation for COPD or pneumonia was significantly elevated among new benzodiazepine users in the healthiest subgroup of COPD patients and this subgroup is least likely to be influenced by confounding by indication [24, 25]. Decreased all-cause mortality was observed among new users in the overall community-dwelling cohort and in the subgroup of individuals with one or more exacerbations requiring presentation to hospital in the year prior to index. Paradoxical associations between a wide variety of medications (including anxiolytics) and mortality in older adults have been reported and interpreted as artefacts of selective prescribing and adherence [30]. All-cause mortality was significantly elevated, however, among new benzodiazepine users in the healthiest COPD patient subgroup, and once again, this is the subgroup that is least likely to be influenced by confounding by indication.

The finding of significantly increased risks for outpatient respiratory exacerbations and emergency room visits for COPD or pneumonia among new benzodiazepine users, consistently across all COPD severity subgroups, including the least severe group, supports the robustness of our results. It has been argued that in nonrandomised outcome studies checking for consistency of outcomes in the healthiest subgroup is important to ensure that results are not influenced by unmeasured confounding [24, 25]. Propensity score matching, which included markers of COPD severity, recent respiratory status stability, healthcare utilisation and overall poor health, allowed us to balance the risk for receiving a benzodiazepine between new and non-users, thus making it less likely that differences in such factors explain our findings. The fact that cohort entry for the unexposed group was defined by medication dispensing may also decrease the

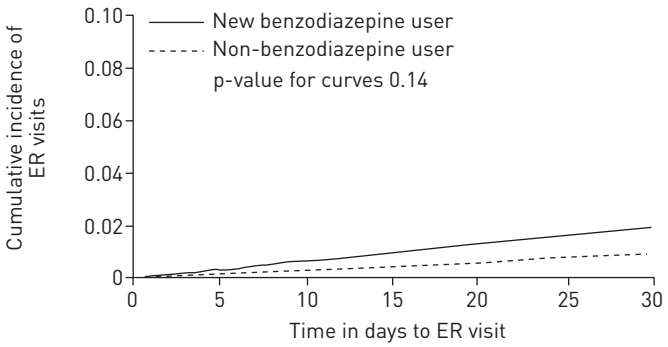

FIGURE 3 Cumulative incidence function curves for emergency room (ER) visits for chronic obstructive pulmonary disease or pneumonia among new and non-benzodiazepine users in the community-dwelling cohort.

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TABLE 3 Risk ratios (RRs) for adverse respiratory outcomes for the matched community-dwelling cohort stratified by chronic obstructive pulmonary disease (COPD) severity

Sensitivity analyses by COPD severity	Benzodiazepine use status	Outpatient respiratory exacerbation		ER visit for COPD or pneumonia		Hospitalisation for COPD or pneumonia		ICU admission during hospitalisation for COPD or pneumonia		All-cause mortality	
		n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
0 exacerbations in the year prior to index	New users	659 (2.37)	1.63 (1.44–1.84)	199 (0.71)	2.46 (1.90–3.18)	244 (0.88)	1.29 (1.07–1.56)	42 (0.15)	1.17 (0.75–1.82)	624 (2.24)	1.19 (1.06–1.34)
	Non-users	405 (1.45)		81 (0.29)		189 (0.68)		36 (0.13)		523 (1.88)	
⩾1 outpatient respiratory exacerbations in the year prior to index	New users	737 (7.60)	1.39 (1.25–1.54)	105 (1.08)	1.84 (1.34–2.54)	137 (1.41)	1.00 (0.79–1.27)	20 (0.21)	0.67 (0.38–1.17)	244 (2.52)	1.10 (0.92–1.32)
	Non-users	532 (5.49)		57 (0.59)		137 (1.41)		30 (0.31)		221 (2.28)	
⩾1 exacerbations requiring presentation to hospital in the year prior to index	New users	985 (8.67)	1.40 (1.27–1.53)	390 (3.43)	1.75 (1.49–2.06)	562 (4.94)	1.05 (0.93–1.17)	71 (0.62)	0.79 (0.58–1.07)	530 (4.66)	0.67 (0.60–0.75)
	Non-users	706 (6.21)		223 (1.96)		537 (4.72)		90 (0.79)		789 (6.94)	

ER: emergency room; ICU: intensive care unit.

likelihood that our findings are explained by differences in health status change or health-seeking behaviour between new and non-benzodiazepine users. In addition, a true relationship between benzodiazepine use and adverse respiratory outcomes in the older COPD population is supported by biological plausibility (benzodiazepine use is associated with negative respiratory physiology markers) [6–12].

There are several limitations. First, as with all observational studies, causation cannot be inferred, as we cannot be certain there were not unmeasured differences between exposed and unexposed subjects, resulting in residual confounding, that may have accounted for our results. Second, patient-level clinical data potentially influencing COPD severity and outcomes, like baseline respiratory and anxiety symptoms, lung function measures and supplemental oxygen use, were not available. However, we provided data on other important measures of COPD severity, including previous history of respiratory exacerbation, which is known to be associated with severity of underlying airflow obstruction [31], risk of future exacerbations [23], and mortality [32], and found positive and consistent results. Third, our COPD definition, while highly specific, had a sensitivity of 58% [16]. While the high specificity of this definition allowed us to be confident that patients included in this study truly had COPD, the lower sensitivity may render our results less generalisable to the entire older COPD population. Fourth, information on indication for benzodiazepine receipt was not captured in the drug database, so we were not able to accurately distinguish adverse respiratory events that followed benzodiazepine dispensation intended for insomnia, psychiatric reasons or refractory dyspnoea. However, we performed a sensitivity analysis stratifying by COPD severity and saw consistent results.

In conclusion, benzodiazepines were associated with significantly increased risk for several serious adverse clinical respiratory outcomes in the older adult COPD population. These findings are concerning, given that benzodiazepines are known to be frequently used among older adults with COPD and in suboptimal ways [2]. The findings suggest that the potential for adverse respiratory outcomes needs to be considered when administering benzodiazepines to older adults with COPD.

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