

Respiratory events associated with concomitant opioid and sedative use among Medicare beneficiaries with chronic obstructive pulmonary disease

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ABSTRACT

Background Opioids and sedatives are commonly prescribed in chronic obstructive pulmonary disease (COPD) patients for symptoms of dyspnoea, pain, insomnia, depression and anxiety. Older adults are advised to avoid these medications due to increased adverse events, including respiratory events. This study examines respiratory event risks associated with concomitant opioid and sedative use compared with opioid use alone in older adults with COPD.

Methods A 5% nationally representative sample of Medicare beneficiaries with COPD and opioid use between 2009 and 2013 was used for this retrospective cohort study. Current and past concomitant use were identified using drug dispensed within 7 days from the censored date: at respiratory event, at death, or at 12 months post index. Concomitant opioid and sedative use were categorised into no overlap (opioid only), 1 to 10, 11 to 30, 31 to 60 and >60 days of total overlap. The primary outcome was hospitalisation or emergency department (ED) visits for respiratory events (COPD exacerbations or respiratory depression). Propensity score matching was implemented and semi-competing risk models were used to address competing risk by death.

Results Among 48 120 eligible beneficiaries, 1810 (16.7%) concomitant users were matched with 9050 (83.3%) opioid only users. Current concomitant use of 1 to 10, 11 to 30 and 31 to 60 days was associated with increased respiratory events (HRs (95% CI): 2.8 (1.2 to 7.3), 9.3 (4.9 to 18.2) and 5.7 (2.5 to 12.5), respectively), compared with opioid only use. Current concomitant use of >60 days or past concomitant use of ≤60 days was not significantly associated with respiratory events. Consistent findings were found in sensitivity analyses, including in subgroup analysis of non-benzodiazepine sedatives. Additionally, current concomitant use significantly increased risk of death.

Conclusion Short-term and medium-term current concomitant opioid and sedative use significantly increased risk of respiratory events and death in older COPD Medicare beneficiaries. Long-term past concomitant users, however, demonstrated lower risks of these outcomes, possibly reflecting a healthy user effect or developed tolerance to the effects of these agents.

Key messages

- This nationally representative study of older Medicare beneficiaries with chronic obstructive pulmonary disease (COPD) examines respiratory event risks associated with current and past concomitant opioid and sedative use compared to opioid use only. Propensity score matching and semi-competing risk models were used to account for potential confounding by indication and competing risk by death.
- There was variation in adverse effects of concomitant opioid and sedative use. Short-term (1 to 10 days) or medium-term (11 to 60 days) current concomitant opioid and sedative use, including both benzodiazepines and non-benzodiazepine sedatives, significantly increased risks of respiratory events; while any medium-term concomitant use increased death, compared with opioid only use. Long-term past concomitant use appears to be associated with reduced risks of these outcomes.
- Concomitant opioid and sedative use should be avoided or closely monitored in older adults with COPD.

INTRODUCTION

The common use of opioids in the Medicare population remains a concern due to adverse risks,¹ including respiratory depression,^{2–6} overdose and death.^{7–10} Risk of these adverse events increases when opioids are used concurrently with other agents with similar effects on the respiratory system.¹¹ In particular, concomitant use of opioids with benzodiazepine and non-benzodiazepine sedatives can lead to an increased risk of respiratory depression.^{12–15} Concomitant use significantly increases risk of overdose or death compared with use of either medication alone.^{16–21} Both opioids and benzodiazepines are recommended to be avoided in older adults according to the American Geriatric Society's Beers Criteria.²²



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Patients with chronic obstructive pulmonary disease (COPD) are more likely to receive opioid prescriptions compared with those without COPD.²³ Opioids are used for a multitude of comorbid conditions and symptoms in COPD patients, including pain, refractory dyspnoea and cough.^{24 25} Between one-fourth to two-thirds of COPD patients have received a prescription for opioids,^{23 25-27} and close to 18% of COPD patients use benzodiazepine or non-benzodiazepine sedatives.²⁸ In the general population, around 1 in 10 opioid users are co-prescribed benzodiazepines or sedatives.²⁹⁻³¹ Among Medicare beneficiaries, about one-fourth have concomitant opioid and sedative prescriptions.^{32 33}

Widespread use of opioids and sedatives in COPD patients is attributable to their higher prevalence of pain, dyspnoea and mental disorders.^{34 35} However, such use is controversial because there is little evidence of benefit or safety associated with opioids and sedatives for dyspnoea.^{36 37} Some studies indicate low doses of opioids or sedatives are beneficial for breathlessness and associate use with no increased respiratory event risks in COPD patients.³⁸⁻⁴¹ Other research has found increased respiratory depression or exacerbations in COPD patients with opioid use.^{25 42 43} Several studies have found benzodiazepines and other sedatives may increase respiratory adverse events in COPD patients.⁴⁴⁻⁴⁶ These mixed findings may be due to a number of factors, including differences in the populations studied, outcome definitions and/or severity of COPD. As well, there is potential confounding by indication when opioids or sedatives are used for dyspnoea, which is a predictor of COPD exacerbation and death.⁴⁷ Studies to date have failed to account for recency of opioid and/or sedative use relative to the respiratory events.⁴⁸ Finally, the competing risk of death plays a key role.⁴⁹ Employing methods to alleviate confounding by indication and competing risks are crucial to generate valid findings in examining risks of opioids and sedatives in COPD patients.

Respiratory event risks associated with concomitant opioid and sedative use are under-investigated in COPD patients, particularly in older adults who commonly use these medications. In particular, the depressive effects of opioids and sedatives on the respiratory system might be a concern in patients with COPD whose respiratory function is already compromised.³⁶ Ekström *et al* found increased risk of death (but did not find increased risk of COPD hospitalisations) in a very severe COPD cohort aged 45 years or older with concomitant opioid and benzodiazepine use.³⁸ In a recent case control study of older Medicare beneficiaries with COPD, increased hospitalisations for respiratory conditions (ie, asthma, COPD, respiratory inflammation, bronchitis) were associated with concomitant opioid and benzodiazepine users.⁵⁰

Our study used a nationally representative Medicare sample to examine the risk of respiratory events in COPD beneficiaries with concomitant opioid and sedative use compared with those with opioid use alone. We applied

a semi-competing risk framework and accounted for the recency of drug exposure to estimate risks associated with concomitant opioid and sedative use.

METHODS

Study design and cohort criteria

This retrospective cohort study used a 5% nationally representative sample of Medicare beneficiary claims data between 1 January 2009 and 31 December 2013. The study cohort included beneficiaries with a diagnosis of COPD and at least one opioid prescription post COPD diagnosis. COPD diagnosis was a flagged variable defined in the Medicare claims by the Center for Medicare and Medicaid Services (the provider of the data), which used Medicare claims since 1999. The algorithm to define COPD (International Classification of Disease, Ninth Revision (ICD-9) codes 490, 491.x, 492.x, 494.x, 496) applied any claim diagnosis and required: (1) at least one inpatient, skilled nursing facility or home health agency claim; or (2) at least two outpatient or carrier claims.⁵¹

The index date was the date of first opioid prescription between 1 January 2010 and 1 January 2013. We excluded beneficiaries under 65 years old. The study used a new user design, requiring beneficiaries to have at least 12 months without opioid or sedative prescriptions prior to the index date. To adequately capture the covariates, exposures and outcomes, beneficiaries were required to have continuous enrolment in Medicare Parts A, B and D for 12 months pre-index and 12 months post-index date, or continuous enrolment until they died within 12 months after the index date. Individuals with Medicare Advantage (Part C) plans were excluded because their claims were not available in the data. In addition, beneficiaries were excluded if they had cancer diagnoses, were admitted to hospice or long-term care during the study period, switched between opioids and sedatives (used both opioids and sedatives but not concomitantly) and received injectable prescription opioids, as conversion factors for injection opioids are different from oral opioids.

Study participants were censored at 12 months post index (those without respiratory events or death), at the time of respiratory event or at death (those without respiratory events). In beneficiaries with respiratory and death within 12 months, time to death is recorded for use in the semi-competing risks model.

Exposure

A list of the medications included in our study is provided in Supplementary 1 (see online supplementary file 1). Opioid and sedative use was identified on each day during follow-up using Medicare Part D data. Concomitant use was defined as overlapping days of use of both opioids and sedatives. We categorised the main exposure variable into five categories: (1) opioid only, (2) concomitant with 1 to 10 days overlap, (3) concomitant with 11 to 30 days overlap, (4) concomitant with 31 to 60 days

overlap and (5) concomitant with >60 days overlap. We additionally used these five categories to define past or current use. Current users were those with concomitant or opioid only use within 7 days of the censored date. Past users had discontinued concomitant or opioid only use at least 7 days prior to the censored date.

We also measured total opioid days supplied and cumulative morphine equivalent dose (MED) to account for the level of exposure to opioids. MED was equal to the quantity unit for each prescription multiplied by dosage strength and morphine milligram equivalency conversion factor.⁵²

Outcomes

Primary study outcomes were hospitalisation and emergency department (ED) visits for respiratory events, including respiratory depression and COPD exacerbations. Respiratory events were captured by the ICD-9 codes 518.81 to 518.84, 518.51 to 518.53, 518.4, 518.5, 799.1, 490, 491, 492, 493, 494 and 496. We recorded death as a competing risk that could preclude the primary outcome.⁴⁹

Covariates

Baselines covariates were defined during the 12 months prior to index date. Covariates measured in the study were demographic factors (age, gender, race), baseline respiratory events, baseline supplemental oxygen use (as a proxy for COPD severity),⁵³ comorbidities known to predict respiratory events as assessed in literature (pain-related conditions, cardiovascular diseases, mental illnesses, musculoskeletal diseases, osteoporosis, chronic kidney disease, peripheral vascular disease and dementia)^{21 25 38} and COPD medications (antibiotics, bronchodilators and oral corticosteroids).

Patient and public involvement

Patients were not involved in the planning, design, data collection or the conduct of this study. The study results will be disseminated through scientific journals.

Statistical analyses

X^2 tests and t-tests were used for categorical and continuous variables, respectively, to compare characteristics of concomitant versus opioid only users.

To alleviate potential confounding by indication when comparing concomitant users with opioid only users, we implemented propensity score matching for the primary analysis.⁵² Logistic regression was used to estimate propensity scores of concomitant use. Potential confounders and opioid total days supplied and cumulative MED were the independent variables in the model (the list of independent variables are provided in the Supplementary 2) (see online supplementary file 2). Due to the imbalance of study participants in the two exposure groups, we operationalised a 1:5 ratio to match concomitant with opioid only users, which was performed without replacement using a caliper size of 0.001. Before

matching, the individuals in the end tails (5th and 95th percentiles) of the propensity score distribution were excluded to reduce unmeasured confounding.⁵⁴ Covariates were examined between the two exposure groups after matching to check for matching performance.

A semi-competing risks Cox proportional hazards model, implemented via the *SemiCompRisks* package in R V.3.5.2, was used to estimate relative risks of respiratory events and death. In the semi-competing risk framework there are terminal events (death) and non-terminal events (respiratory). The framework aims to address the semi-competing risk of respiratory events by death (ie, death prevents respiratory events from occurring but not vice versa). Specifically, the semi-competing risks framework addresses a potential dependence between respiratory events and death by adding a patient-specific frailty to the standard proportional hazard regression model. A more detailed description of the semi-competing risks framework is available from Haneuse and colleagues,^{55 56} and an example of its application is described elsewhere.⁵⁷ To compare with the results of semi-competing risk models, we also implemented standard Cox proportional hazards (censoring death) and Fine-Gray competing-risk models.⁴⁹

We also conducted several sensitivity analyses that: (1) defined current use as use within 30 days of the censored date, (2) included subgroup analyses among more severe COPD beneficiaries who had baseline oxygen supplementation, (3) estimated multivariable models using all eligible beneficiaries without propensity score matching and (4) conducted subgroup analysis of only non-benzodiazepine sedative concomitant use, with users of benzodiazepines to be excluded.

Analyses were implemented using SAS V.9.4 and R V.3.5.2. HR and 95% CIs were reported.

RESULTS

A total of 48 120 beneficiaries with COPD and opioid use met the study criteria, 84% of whom were white and 86% were female, with mean age of 77 years (SD of 7). Among these, 2296 (4.8%) beneficiaries had concomitant opioid and sedative use, while the remaining 45 824 (94.2%) beneficiaries used only opioids.

Concomitant users were more likely to be younger and female than opioid only users (table 1). Beneficiaries with opioid only use had higher baseline respiratory event rates, cardiovascular diseases, chronic kidney disease, pain conditions, musculoskeletal diseases, osteoporosis and dementia than concomitant users. In addition, the opioid only group used more baseline anticholinergics, beta-agonists and inhaled corticosteroids than concomitant users. Both groups had similar use of oxygen supplementation, antibiotics, theophylline and oral corticosteroids. Concomitant users had higher cumulative MED and total opioid days supplied than opioid only users (table 1).

After propensity score matching, 1810 concomitant users were matched with 9050 opioid only users

Table 1 Characteristics of study cohort before and after matching

Covariates	Before matching			After matching		
	Concomitant n=2296	Opioid only n=45 824	P value	Concomitant n=1810	Opioid only n=9050	P value
Age (years)			<0.01			0.79
65–74	1200 (52.3)	18 691 (40.8)		805 (44.5)	4103 (45.3)	
75–84	836 (36.4)	19 377 (42.3)		758 (41.9)	3724 (41.1)	
≥85	260 (11.3)	7756 (16.9)		247 (13.6)	1223 (13.5)	
Females	1579 (68.8)	29 412 (64.2)	<0.01	1212 (67.0)	6197 (68.5)	0.69
Race			<0.01			0.68
White	1936 (84.3)	37 759 (82.4)		1490 (82.3)	7506 (82.9)	
Black	155 (6.8)	4350 (9.5)		151 (8.3)	753 (8.3)	
Hispanic	96 (4.2)	1715 (3.7)		84 (4.6)	397 (4.4)	
Asian	109 (4.7)	2000 (4.4)		85 (4.7)	394 (4.4)	
Comorbidities						
Respiratory events*	568 (24.7)	17 511 (38.2)	<0.01	525 (29.0)	2596 (28.7)	0.88
Diabetes	329 (14.3)	10 514 (22.9)	<0.01	317 (17.5)	1538 (17.0)	0.59
Heart failure	196 (8.5)	6049 (13.2)	<0.01	180 (9.9)	924 (10.2)	0.10
Ischaemic heart disease	367 (16.0)	11 327 (24.7)	<0.01	342 (18.9)	1686 (18.6)	0.94
Acute myocardial infarction	19 (0.8)	564 (1.2)	0.08	16 (0.9)	91 (1.0)	0.63
Stroke	73 (3.2)	2414 (5.3)	<0.01	70 (3.9)	360 (4.0)	0.78
Hypertension	752 (32.8)	23 846 (52.0)	<0.01	696 (38.5)	3546 (39.2)	0.73
Hyperlipidaemia	632 (27.5)	20 712 (45.2)	<0.01	591 (32.7)	2940 (32.5)	0.79
Peripheral vascular disease	202 (8.8)	6075 (13.3)	<0.01	183 (10.1)	944 (10.4)	0.68
Chronic kidney disease	204 (8.9)	5247 (11.5)	<0.01	184 (10.2)	892 (9.9)	0.69
Pain†	382 (16.6)	10 123 (22.1)	<0.01	348 (19.2)	1765 (19.5)	0.50
Musculoskeletal disease‡	422 (18.4)	12 439 (27.1)	<0.01	395 (21.8)	1979 (21.9)	0.99
Osteoporosis	148 (6.4)	4902 (10.7)	<0.01	139 (7.7)	738 (8.2)	0.93
Mental disorders§	299 (13.0)	5198 (11.3)	0.01	237 (13.1)	1163 (12.9)	0.89
Dementia	64 (2.8)	1943 (4.2)	<0.01	62 (3.4)	287 (3.2)	0.58
Medication use						
Antibiotics	368 (16.0)	7270 (15.9)	0.84	277 (15.3)	1403 (15.5)	0.83
Anticholinergic	218 (9.5)	7016 (15.3)	<0.01	210 (11.6)	1004 (11.1)	0.53
Beta-agonists	544 (23.7)	14 214 (31.0)	<0.01	496 (27.4)	2455 (27.1)	0.81
Inhaled corticoids	544 (23.7)	13 207 (28.8)	<0.01	473 (26.1)	2357 (26.0)	0.56
Combined corticoids	267 (11.6)	7419 (16.2)	<0.01	250 (13.8)	1228 (13.6)	0.78
Oral corticoids	557 (24.3)	11 733 (25.6)	<0.01	450 (24.9)	2271 (25.1)	0.93
Theophylline	34 (1.5)	653 (1.4)	0.19	31 (1.7)	142 (1.6)	0.30
Oxygen supplement	355 (15.5)	5947 (13.0)	0.15	256 (14.1)	1284 (14.2)	0.84
Cumulative opioid MED (mg)¶			<0.01			0.85
<150	44 (1.9)	9160 (20.0)		43 (2.4)	219 (2.4)	
150–350	211 (9.2)	13 772 (30.1)		211 (11.7)	1031 (11.4)	
350–900	494 (21.5)	10 788 (23.5)		493 (27.2)	2485 (27.5)	
900–2250	592 (25.8)	6795 (14.8)		547 (30.2)	2764 (30.5)	
>2250	955 (41.6)	5309 (11.6)		516 (28.5)	2551 (28.2)	
Opioid total days supplied			<0.01			0.97
1–10	192 (8.4)	20 594 (44.9)		191 (10.6)	965 (10.7)	

Continued

Table 1 Continued

Covariates	Before matching		P value	After matching		P value
	Concomitant n=2296	Opioid only n=45 824		Concomitant n=1810	Opioid only n=9050	
11–30	439 (19.1)	11 429 (24.9)		439 (24.3)	2197 (24.3)	
30–60	387 (16.9)	5494 (12.0)		379 (20.9)	1893 (20.9)	
62–90	283 (12.3)	2263 (4.9)		221 (12.2)	1041 (11.5)	
>90	995 (43.3)	6044 (13.2)		580 (32.0)	2954 (32.6)	

*COPD exacerbation and respiratory distress.

†Chronic pain, fibromyalgia and migraine.

‡Arthropathy, arthritis, lupus and rheumatoid arthritis.

§Depression, anxiety, bipolar and schizophrenia.

¶Morphine equivalent dose.

COPD, chronic obstructive pulmonary disease; MED, morphine equivalent dose.

(figure 1). All baseline covariates, including opioid total days supplied and cumulative MED, were similar between the two matched groups (table 1). Mean (median) cumulative MED and total opioid days supplied in the matched cohort were 3021 (1125) mg and 98 (50) days, respectively. Compared with non-matched beneficiaries (n=37 260), matched beneficiaries (n=10 860) were younger, more likely to be female, had fewer comorbidities, and higher cumulative MED and total opioid days supplied (see online supplementary file 2).

In the propensity score matched cohort, among concomitant users there were 319 (17.6%) beneficiaries who experienced respiratory events without death. Mean (median) time to respiratory events was 146 (127), 157 (170), 126 (81), 124 (92), 168 (175) days respectively for opioid only users and concomitant users of 1 to 10, 11 to 30, 31 to 60 and >60 days. In addition, 53 (2.9%) beneficiaries died after respiratory events and 59 (3.3%) died without having respiratory events. In opioid only users,

16.2% had respiratory events without death, 2.7% died after respiratory events and 3.3% died without having respiratory events (table 2).

Primary analyses

Table 3 shows the HRs of respiratory events and deaths from three models: (1) Cox proportional hazards, (2) Fine-Gray competing-risk and 3) semi-competing risks. Across all models, risks of respiratory events and death increased with total days of current concomitant use, then decreased in beneficiaries with 60+ days of current concomitant use, compared with opioid only users.

In the semi-competing risks models, beneficiaries with 11 to 30 days of current concomitant use had highest risks of respiratory events (HR 9.3, 95% CI 4.9 to 18.2), and those with 31 to 60 days of current concomitant use were at the greatest risk of death before respiratory events (HR 10.2, 95% CI 3.4 to 26.3). The risk of death after respiratory events was increased (HR 2.8, 95% CI 1.1 to 6.5) in current concomitant users of 11 to 30 days compared with opioid only users, as was the risk of death without respiratory events (HR 8.3, 95% CI 2.9 to 20.1). Past concomitant short-term use (<11 days) and past concomitant medium-term use (11 to 60 days) demonstrated no significant effect on respiratory events but on death compared with past use of opioid only. In addition, long-term (>60 days) past concomitant users had lower risks of respiratory events (HR 0.6, 95% CI 0.3 to 0.9) and death (HR 0.2, 95% CI 0.04 to 0.9) than past opioid only users.

Cox regression and Fine-Gray competing-risk models also show increased risks of respiratory events among concomitant users of 11 to 60 days (table 3).

Cumulative MED was consistently associated with respiratory events in a dose-response manner, with risks of respiratory events increasing when cumulative MED increased. The risk of death was highest among those with cumulative MED of 350 mg to 900 mg (table 3).

Sensitivity analyses

When extending the time window to define the current use of drugs to 30 days from the censored date, results

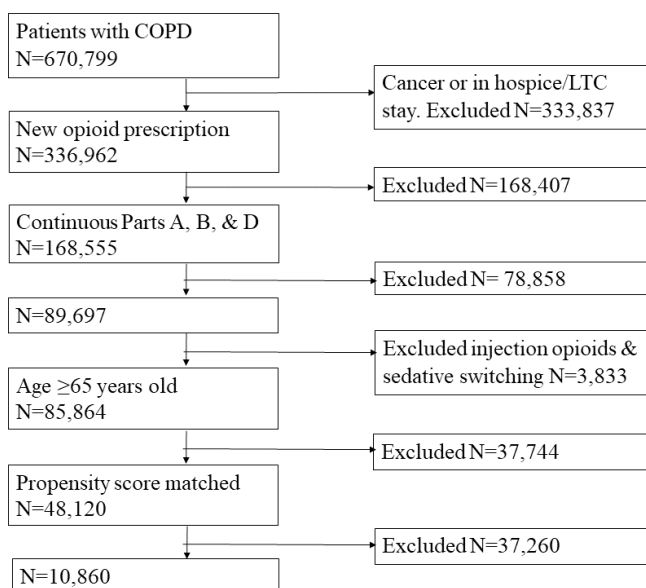


Figure 1 Flow chart of the study cohort. COPD, chronic obstructive pulmonary disease; LTC, long-term care.

Table 2 Respiratory events and death within 12 months follow-up in the matched cohort (n=10 860)

N (column %)	Concomitant users (n=1810)	Opioid only users (n=9050)	Total (n=10 860)
Respiratory events without death	319 (17.6%)	1466 (16.2%)	1785 (16.8%)
Respiratory events with death	53 (2.9%)	244 (2.7%)	297 (2.7%)
Death without respiratory events	59 (3.3%)	296 (3.3%)	355 (3.3%)

Respiratory events=COPD exacerbation or respiratory depression.
COPD, chronic obstructive pulmonary disease.

were relatively similar compared with the main analysis. Current concomitant users with 11 to 30 days had the highest HR of respiratory events (HR 9.5, 95% CI 4.9 to 18.6), and 31 to 60 days of current concomitant users had highest risk of death (HR 9.6, 95% CI 3.3 to 25.3). Past concomitant users of 60+ days had significantly lower risks of respiratory events and death (see online supplementary file 3).

In the subgroup analysis among COPD beneficiaries with oxygen supplementation at baseline, current concomitant users with 1 to 10 days had highest risks of respiratory events (HR 13.3, 95% CI 2.9 to 74.5) and

death (HR 20.1, 95% CI 1.9 to 157.8) (see online supplementary file 3).

In the third sensitivity analysis using multivariate analyses to include the full cohort, instead of matching, respiratory event risks were still increased in concomitant users, but the effect size was lower than in the main analyses, with a HR of 5.4 (95% CI 3.1 to 9.6).

We found similar findings compared with the main findings about respiratory event and death risks in those with concomitant use of non-benzodiazepine sedatives. HR in beneficiaries with 11 to 30 days concomitant use was highest (HR 7.6, 95% CI 1.9 to 25.9).

Table 3 Associations of concomitant opioid and sedative use with respiratory events and death (HRs and 95% CI)

Covariates	Cox model		Competing-risk		Semi-competing risk		
	Respiratory events	Death	Respiratory events	Death	Respiratory events	Death before respiratory events	Death after Respiratory events
Past concomitant users (days)*							
1–10	1.050 (0.858–1.285)	0.702 (0.465–1.060)	1.165 (0.945–1.437)	0.702 (0.465–1.059)	1.024 (0.765–0.357)	0.826 (0.459–1.388)	0.444 (0.195–0.902)
11–30	0.884 (0.707–1.1006)	0.803 (0.533–1.210)	0.879 (0.689–1.122)	0.803 (0.534–1.208)	0.827 (0.609–1.105)	0.597 (0.300–1.079)	0.944 (0.496–1.693)
31–60	0.944 (0.695–1.283)	1.261 (0.777–2.045)	0.861 (0.608–1.222)	1.261 (0.779–2.039)	0.888 (0.577–1.369)	0.972 (0.414–1.970)	1.557 (0.666–3.221)
>60	0.724 (0.497–1.054)	0.401 (0.149–1.075)	0.786 (0.535–1.153)	0.401 (0.150–1.068)	0.557 (0.336–0.909)	0.244 (0.035–0.858)	0.527 (0.075–2.000)
Current concomitant users (days)*							
1–10	1.511 (0.937–2.437)	1.245 (0.516–3.005)	1.641 (0.989–2.720)	1.245 (0.509–3.043)	2.801 (1.173–7.268)	3.303 (0.826–11.168)	0.233 (0.006–1.416)
11–30	3.161 (2.291–4.360)	3.266 (1.945–5.460)	2.529 (1.735–3.688)	3.266 (1.916–5.569)	9.281 (4.905–18.249)	8.314 (2.945–20.134)	2.806 (1.120–6.558)
31–60	2.223 (1.458–3.391)	3.560 (1.953–6.489)	1.810 (1.116–2.934)	3.560 (1.983–6.695)	5.714 (2.462–12.482)	10.185 (3.459–26.342)	2.529 (0.699–7.762)
>60	1.274 (0.934–1.739)	1.400 (0.782–2.506)	1.164 (0.826–1.641)	1.400 (0.788–2.487)	1.212 (0.762–1.917)	0.770 (0.216–1.986)	1.827 (4.003)
Cumulative MED (mg)†							
150–350	1.543 (1.053–2.263)	1.676 (0.868–3.236)	1.506 (0.994–2.281)	1.761 (0.867–3.241)	1.925 (1.106–3.094)	2.3797 (0.947–8.234)	1.077 (0.419–3.198)
350–900	1.716 (1.188–2.478)	1.712 (0.906–3.232)	1.721 (1.155–2.564)	1.712 (0.907–3.231)	2.177 (1.250–3.456)	2.680 (1.116–9.228)	0.853 (0.348–2.422)
900–2250	1.750 (1.212–2.526)	1.516 (0.803–2.865)	1.791 (1.202–2.668)	1.516 (0.803–2.863)	2.245 (1.297–3.559)	2.286 (0.951–7.944)	0.756 (0.672–2.179)
>2250	1.970 (1.364–2.845)	1.291 (0.680–2.451)	2.128 (1.428–3.172)	1.291 (0.680–2.450)	2.464 (1.416–3.895)	1.944 (0.794–6.717)	0.583 (0.238–1.655)

*Reference group is past opioid only users.

†Reference group is cumulative use <150 mg. MED, morphine equivalent dose.

Past concomitant use was not associated with respiratory events or death. Cumulative MED was significantly associated with respiratory events and death with a dose-response effect in the third sensitivity analysis 3 and 4, but not in sensitivity analyses 1 and 2 (see online supplementary file 3).

DISCUSSION

In this national study of Medicare beneficiaries with COPD, current concomitant use of opioids and sedatives significantly increased risks of respiratory events, including COPD exacerbations and respiratory depression. In addition, current concomitant use was associated with an almost 10-fold increased risk of death compared with opioid use alone. There was a duration-response of the effects, with risks increasing from short (1 to 10 days) to medium (11 to 60 days) duration of concomitant use, while it was insignificant in longer (>60 days) current concomitant use.

The recency of concomitant opioid and sedative use (e.g., the time between the last concomitant exposure and the respiratory events) is crucial in evaluating risks. In this study, short and medium duration of past concomitant use was not associated with respiratory events or death, however, long-term (>60 days) past concomitant use decreased these risks. The reduced risks with long-term past and current concomitant use is likely the result of a healthy user effect. Healthy user effect relates to multiple characteristics of the patients that make them less likely to have adverse events, including disease severity, cognitive functions, frailty or adherence. New user design, propensity score matching and active comparator groups could alleviate healthy user effect biases.⁵⁸ In addition, the reduced risk associated with long-term concomitant use may be attributable to the ability of certain patients to develop tolerance to opioids and sedatives as suggested in prior literature.^{59 60}

We also found increased risks of respiratory events when cumulative MED increased. This is indicative of potential opioid dosing effects in less severe and healthier COPD patients in the primary analysis. Sensitivity analyses demonstrated no associations when defining drug exposure recency as within 30 days, or when restricting to more severe COPD patients with oxygen supplementation.

Death is an important competing outcome to consider, as it would have precluded the occurrence of respiratory events in some patients.⁴⁹ Appropriate approaches to account for the semi-competing nature between respiratory events (non-terminal events) and deaths (terminal events) are necessary to achieve valid estimation of respiratory event risks. In this study, traditional Cox regression and Fine-Gray competing-risk models were found to underestimate the risks of the non-terminal events compared with the findings in semi-competing risk models. The use of a semi-competing risk framework facilitates a more proper approach for competing events between respiratory events and death, and is appropriate for broader use when compared with Cox proportional hazards and Fine-Gray competing-risk models.

Despite prior literature on risks of opioid and benzodiazepines in COPD patients,^{12 16} this is the first study to examine concomitant use of opioids with both benzodiazepines and non-benzodiazepine sedatives in older adults with COPD. Concomitant opioid and benzodiazepine use was associated with strong adverse effects including respiratory depressions, overdoses and death in prior literature.^{12 16} Both benzodiazepines and other sedatives have similar pharmacological effects on depressive respiratory symptoms.⁶¹ In the subgroup analysis of only concomitant use of opioids and non-benzodiazepine sedatives, we also found increased respiratory event risks. Thus, extending the investigation to concomitant use of opioids and all sedatives, not just benzodiazepines, makes this study highly relevant, especially when sedative use is common in older Medicare beneficiaries with COPD.

Ekström *et al* investigated risks of concomitant opioids and benzodiazepines in a very severe COPD cohort with oxygen supplementation.⁶² The authors found low doses of concomitant use were associated with death but not with COPD hospitalisations. Additionally, we found similar but stronger effects than the findings in a study of older Medicare beneficiaries with COPD by Baillargeon *et al*.⁵⁰ The following strengths of our study help explain differences in findings compared with these two studies. For one, both studies only included benzodiazepine sedatives. Second, our study used a new-user study design to avoid prevalent user bias, whereas Ekström and Baillargeon used prevalent users. Third, in addition to our new-user design, the use of propensity score matching reduced confounding by indication—a main challenge when examining concomitant use of opioids and sedatives in COPD patients. Fourth, the semi-competing risk framework used in this study properly accounts for the competing risk nature of respiratory events by death. Finally, we defined recency of drugs when examining adverse events which has been recommended as standard in pharmacoepidemiology studies.⁴⁸ Inclusion of both current and past use in our study allows for more valid estimates of respiratory event risks based on the time of drug exposure.

Findings of our study have several implications. Our results lend support to the recommendation to avoid these drugs in older adults per the Beers criteria, particularly their concomitant use, even though concomitant use of opioids and sedatives in older Medicare beneficiaries with COPD is common. In addition, a significant proportion of beneficiaries had high cumulative MED use, which is more likely to increase risk of adverse events. Thus, more careful prescription management programmes for older adults with COPD may be needed. Physicians who prescribe opioids or sedatives to older COPD patients should carefully assess whether older beneficiaries are already prescribed these medications by others providers.

In addition, there is variation in effects of concomitant use, as illustrated by the wide intervals of estimates, the opposite effects in past and current concomitant use and the slight variation of findings across sensitivity analyses.



This variation in effects of concomitant use is likely due to the heterogeneous clinical profile in COPD patients.⁶³ Thus, if opioids or sedatives are needed in older COPD patients, a personalised approach should be considered, along with close monitoring for possible adverse events. Finally, monitoring of opioid doses should be considered due to its impact on adverse events. Further research on effects of opioid and sedative dosing on COPD patients also is necessary.

Several limitations of this study require acknowledgement. First, this study uses administrative claims data; thus important predictors of COPD respiratory outcomes, such as smoking, lung function (forced expiratory volume in one second), frailty and body mass index could not be assessed, resulting in potential unmeasured confounding. Second, use of opioids and sedatives were assumed to be what was observed in the claims; however, patients may not have taken the medications as prescribed. To mitigate this problem, sensitivity analyses were implemented to define different time windows of current versus past drug exposure. Third, our study could not account for effects of sedative dose as no consistent conversion factors are available for all sedative agents. Fourth, there is potential bias if patients experienced hospitalisation for non-respiratory events during follow-up. Fifth, propensity score matching balanced opioid use and cumulative MED between concomitant and opioid only groups; however, this approach does not guarantee complete avoidance of immortal time bias in those who used opioids only and died before becoming concomitant users. Additional adjustment of opioid cumulative MED after matching was implemented to further reduce this residual bias. Finally, this study only included older Medicare beneficiaries who would be at higher risks of adverse events by opioids and sedatives than younger individuals. Future research should extend the study to other populations to examine the generalisability of these findings.

CONCLUSIONS

Current concomitant use of opioids and sedatives significantly increased respiratory event risks and death in older Medicare beneficiaries with COPD. However, long-term past concomitant users demonstrated lower risks. Understanding different factors associated with potential risks is critical to inform the use of opioids and sedatives in older adults with COPD.

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