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Use of Opioids or Benzodiazepines and Risk of Pneumonia in Older Adults: A Population-Based Case-Control Study

Sascha Dublin, MD, PhD^{1,2}, Rod L. Walker, MS¹, Michael L. Jackson, PhD, MPH¹, Jennifer C. Nelson, PhD^{1,3}, Noel S. Weiss, MD, PhD², Michael Von Korff, ScD^{1,4}, and Lisa A. Jackson, MD, MPH^{1,2}

¹Group Health Research Institute, Seattle, Washington

²Department of Epidemiology, University of Washington, Seattle, Washington

³Department of Biostatistics, University of Washington, Seattle, Washington

⁴Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington

Abstract

OBJECTIVES—To examine whether use of opioids or benzodiazepines is associated with increased risk of community-acquired pneumonia in older adults.

DESIGN—Population-based case-control study.

SETTING—An integrated healthcare delivery system.

PARTICIPANTS—Community-dwelling, immunocompetent adults aged 65–94 from 2000–2003. Presumptive pneumonia cases were identified from health plan automated data and validated through medical record review. Two matched controls were selected for each case with pneumonia, matched on age, sex and calendar year.

MEASUREMENTS—Information about opioid and benzodiazepine use came from computerized pharmacy data. Information on covariates including comorbid illnesses and functional and cognitive status came from medical record review and electronic health data.

RESULTS—1039 validated cases of pneumonia and 2022 matched controls were identified. 13.9% (144/1039) of cases and 8.0% (161/2022) of controls used prescription opioids (adjusted OR 1.38, 95% CI 1.08 to 1.76, vs. nonuse). Risk was highest for opioids categorized as immunosuppressive based on immunologic studies (OR 1.88 [95% CI, 1.26 to 1.79] vs. nonuse), while for non-immunosuppressive opioids the OR was 1.23 (95% CI, 0.89 to 1.69). Risk was highest in the first 14 days of use (OR 3.24 [95% CI, 1.64 to 6.39] vs. nonuse). For long-acting opioids, the OR was 3.43 [95% CI, 1.44 to 8.21] vs. nonuse, while for short-acting opioids it was

Corresponding author: Sascha Dublin, Group Health Research Institute, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101-1448. Phone 206-287-2870; Fax 206-287-2871. dublin.s@ghc.org. Alternate corresponding author: Rod Walker, Group Health Research Institute, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101-1448. Phone 206-287-2895; Fax 206-287-2871. walker.rl@ghc.org.

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Conflict of Interest

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1.27 [95% CI, 0.98 to 1.64]. No increased risk was seen for current benzodiazepine use (OR 1.08, 95% CI 0.80 to 1.47, compared to nonuse).

CONCLUSION—Use of opioids but not benzodiazepines was associated with increased pneumonia risk. The differences in risk seen for different opioid regimens warrant further study.

Keywords

pneumonia; epidemiology; opioids; adverse drug effects; benzodiazepines

INTRODUCTION

Prescription opioids and benzodiazepines are widely used, opioids for acute or chronic pain and benzodiazepines for conditions including insomnia and anxiety. In 2002, 18% of U.S. adults received at least one opioid prescription, and the prevalence of use increased with age.¹ An estimated 2 million U.S. adults over age 65 are using opioids long-term for non-cancer pain.² These numbers may rise due to recommendations from the American Geriatrics Society promoting opioids over nonsteroidal anti-inflammatory drugs for older adults with moderate to severe persistent pain.³ There are few recent data for benzodiazepine use, but a 1998 study found that one in 10 people over 65 in the U.S. was using a benzodiazepine.⁴

Both opioids and benzodiazepines plausibly could increase risk of pneumonia, a common infection with serious consequences in older adults. Both medication classes cause sedation, which may increase the risk of aspiration,⁵ and both can cause respiratory depression. Moreover, in human and animal studies, some opioids suppress the immune system. They inhibit macrophages and natural killer cells,^{6–11} alter cytokine production,^{9, 11, 12} and impair migration of macrophages and neutrophils.^{12–14} In a mouse model of pneumonia due to *Streptococcus pneumoniae*, mice pre-treated with morphine had increased pulmonary inflammation, bacterial dissemination, and mortality compared to mice pre-treated with placebo.^{12, 14} These effects appeared to be mediated by a decrease in chemokines including TNF- α , IL-1, IL-6, and MIP-2 in bronchoalveolar lavage fluid and lung tissue.^{12, 14} *In vitro*, alveolar macrophages treated with morphine released less MIP-2, a chemoattractant for neutrophils.¹⁴ Morphine inhibited NF-kB-dependent gene transcription in these cells, suggesting a mechanism for these effects.¹⁴ Thus, immunologic studies have demonstrated plausible biologic mechanisms by which opioids may increase infection risk, including risk of pneumonia.

Particularly noteworthy are immunologic studies showing that immune effects may differ across opioid medications. Among commonly used opioids, several suppress the immune system (e.g. morphine, codeine and fentanyl), while others appear not to (e.g. hydrocodone and oxycodone).^{11, 15–17} This has important implications for clinical practice, because in many cases, physicians could readily select a non-immunosuppressive opioid in place of one that is believed to be immunosuppressive. Despite an extensive immunologic literature, the association between opioid use and infection has scarcely been examined in human clinical or epidemiologic studies. The only two studies that have been conducted^{18, 19} provide limited insight because they examined specialized populations and included few patients with infections. Neither study attempted to classify opioids according to their immunosuppressive effects. Three studies have examined the association of pneumonia with benzodiazepine use, with conflicting results.^{20–22}

We examined the association between use of opioids or benzodiazepines and pneumonia risk in a population-based case-control study in which all pneumonia cases were validated and information on potential confounders came from detailed medical record review.²³ We

hypothesized that pneumonia risk would be elevated among people using benzodiazepines and opioids compared to nonusers, and that risk would be highest for long-acting opioids and opioids deemed to be immunosuppressive in prior immunologic studies.

METHODS

Overview and Setting

We analyzed existing data from a nested case-control study of community-acquired pneumonia (CAP) among older adults within Group Health (GH), an integrated healthcare delivery system. This study was approved by the GH Human Subjects Review Committee with a waiver of consent.

Source population

The study population included GH members' ages 65–94 years with at least 2 years of continuous enrollment who were community-dwelling and not immunosuppressed. Eligibility was based on computerized pharmacy, laboratory, and utilization data and confirmed by medical record review. Immunosuppression was defined as having serious cancer, recent cancer treatment, or chronic kidney disease, or receiving certain immunosuppressive medications or medications for human immunodeficiency virus (details in Appendix Table 1, online). Because the original study²³ examined pneumonia risk in relation to influenza vaccination, eligibility was initially determined as of September 1 in each study year (2000, 2001 and 2002). Because we wished to examine opioid and benzodiazepine use shortly before pneumonia onset, we also excluded people who based on computerized diagnosis and pharmacy data developed the above exclusionary conditions during follow-up in each study year. These people were considered eligible up until the date they developed an exclusionary condition but were excluded from the study population thereafter.

Selection of cases and controls

The methods used to identify and validate pneumonia cases have been described previously.²⁴ We identified presumptive cases using International Classification of Diseases, version 9 codes (480 to 487.0 or 507.0) and validated them through review of chest radiograph reports and hospitalization records. Medical record abstractors reviewed the electronic text of chest radiograph reports for descriptions of qualifying findings such as an infiltrate or consolidation. We did not re-interpret the radiographs themselves. Many GH patients who require hospitalization receive this care outside of GH. For these patients, we did not have access to radiograph reports but rather to hospital admission, discharge, and consultation notes. Cases were judged to have pneumonia if a chest radiograph report described a parenchymal infiltrate not known to be chronic or, for hospitalized cases, if the final physician assessment was that pneumonia caused the illness present at admission. Cases of hospital-acquired pneumonia or massive aspiration were excluded. Massive aspiration was identified through medical record review and was considered to be present if a person with no prior evidence of acute respiratory illness developed pneumonia after a sudden, massive insult (such as near-drowning, loss of consciousness due to a stroke or seizure, or choking on food).

Because of the aims of the original study, cases were identified from September 1 until the end of influenza season in each study year (2000–1, 2001–2, and 2002–3).²³ Cases were assigned an index date representing the date of pneumonia diagnosis, defined as the date of the first positive chest radiograph or, for hospitalized cases without a positive chest radiograph at GH, the date of hospital admission. For people with multiple episodes of pneumonia, we included only the first episode. Up to 2 controls were selected for each case

matched on age, sex, and calendar year. Controls were required to have survived and remained enrolled in GH through their matched case's diagnosis date (incidence density sampling.) Controls were assigned the same index date as their matched case. Figure 1 shows the flow of potential subjects through the study.

Measures of drug exposure

GH's computerized pharmacy database provided information on prescription fills including medication name, strength, route of administration, date dispensed, quantity dispensed, and days supplied. In prior studies, 96% of GH members in this age group reported filling all or almost all of their prescriptions at GH pharmacies.²⁵ Oral, transdermal, and sublingual medications were included. Opioids used in cough suppressants were excluded because they might have been prescribed for pneumonia symptoms. We defined "current use" as having filled 1 or more prescriptions between 5 and 60 days prior to index date. Fills in the 4 days prior to index were excluded because these may have been prescribed for symptoms of pneumonia. Thus, for example, a person who filled an opioid prescription 3 days prior to index date but had no other fills in the prior 12 months would have been characterized as a nonuser. We chose a relatively liberal definition of "current use" to allow for sporadic or inconsistent use. "Past use" was defined as filling at least one prescription between 61 and 365 days prior to index date but none from 5–60 days before index date, while "nonuse" was defined as filling no prescriptions from 5–365 days before index.

For current users, we defined initiation of use as follows. Each prescription fill was assigned a run-out date based on the date of the fill and the days supplied. Use was considered continuous if the next prescription was filled no later than 90 days after the previous fill's run-out date. We chose 90 days to allow for intermittent or sporadic use, because based on the immunologic literature we believed it was important to identify "new initiators" accurately, including only people who truly were initiating these medications after a period of non-use. We defined the date of initiation as the date of the first fill in the most recent episode of continuous use.

We classified opioid medications as long-acting or short-acting and, based on prior immunologic studies, as immunosuppressive or non-immunosuppressive (Table 1).^{11, 15, 16, 26–28} For current opioid users who initiated use more than 90 days prior to index date (chronic long-term users), we estimated their daily dose (EDD) in morphine equivalents as follows. We identified prescription fills which overlapped the 90-day window prior to index date. For each fill, we multiplied the number of pills by the strength and by a conversion factor to calculate morphine equivalent doses (MEDs).²⁸ We then summed the MEDs across prescriptions (accounting for the fact that some prescriptions overlapped this time period only partially) and divided by 90 days (the length of the time window) to get each current user's EDD. We did not calculate an EDD for people who initiated use less than 90 days prior to index date because this would require strong assumptions about intensity of use. We categorized the EDD as 1 to 19 mg, 20 to 49 mg, or ≥ 50 mg daily in morphine equivalents.

Benzodiazepines were classified according to half-life (Appendix Table 2, online). To measure intensity of use, we converted benzodiazepine prescriptions to total standardized doses (TSD) based on the minimum effective daily dose reported in standard references²⁹ and summed TSD over the 12 months prior to index date. Among current benzodiazepine users, "heavy use" was defined as receiving at least 150 TSD in the prior 365 days.

Measurement of other covariates

Information about other characteristics came from electronic databases and detailed medical record review. The medical record review focused on the 2 year period prior to September 1 of each year (defined hereafter as the baseline period) and was conducted in the same manner for cases and controls. It assessed demographic characteristics, height and weight, smoking status, and the presence and severity of health conditions hypothesized to be associated with pneumonia risk. We assessed the severity of comorbid illnesses using measures such as long-term steroid use for lung disease (receiving oral steroids to be taken at least 3 times per week for at least 3 months), home oxygen use, and whether ejection fraction (EF) was measured. Functional status measures were defined based on documentation in the chart and included need for assistance with ambulation or bathing, use of home health services, and whether a subject was ever described as frail by medical personnel. Cognitive status was defined based on the presence of a physician diagnosis of dementia in the chart. We obtained information from computerized pharmacy data about medications expected to be associated with pneumonia risk, including medications for chronic lung or heart disease. Electronic data sources provided information about the number of outpatient visits in the 1 year prior to September 1 of each year.

Analysis

We first examined characteristics of pneumonia cases and controls, calculating proportions for categorical variables and medians and interquartile ranges for continuous variables. Similar analyses explored characteristics associated with current use of opioids or benzodiazepines among control subjects. We used multivariable conditional logistic regression to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of CAP, comparing current use of each medication class to nonuse. Opioid and benzodiazepine use were examined in the same model, so risk estimates for each medication class are adjusted for the other. We selected the following potential confounders for our final model *a priori*, based on review of the literature and clinical plausibility: asthma, chronic obstructive pulmonary disease (COPD), COPD hospitalization, use of home oxygen, long-term steroid use for lung disease, whether forced expiratory volume in one second (FEV₁) was measured, congestive heart failure (CHF), CHF hospitalization, whether EF was measured, stroke, number of outpatient visits in 1-year baseline period (a continuous variable), need for assistance with ambulation or bathing, dementia, and use of inhaled bronchodilators, inhaled corticosteroids, oral corticosteroids, or furosemide. To test whether the association between opioid or benzodiazepine use and pneumonia was modified by use of the other drug class, we included interaction terms in the model and used an omnibus Wald test to assess statistical significance.

Additional analyses examined the risk of pneumonia according to medication half-life, recency of initiation, and intensity of use. For opioids, we also examined risk for groups categorized by their immunosuppressive effects based on the published immunologic literature.

We carried out sensitivity analyses to assess the robustness of our results. First, we applied a stricter definition of “current use,” in which current use was defined as having filled an opioid prescription which would have been expected to last beyond 7 days prior to index date. The goal was to increase the likelihood that “current users” were using opioids on or shortly before the index date. Second, to disentangle the potential effects of opioid half-life vs. immunosuppression, we repeated the analysis of immunosuppressive versus non-immunosuppressive opioids stratified by opioid half-life. Third, we performed sensitivity analyses excluding people with any use of oral corticosteroids during baseline or follow-up. We did this to remove any bias which could arise if patients with an inflammatory condition

experienced a disease flare and were prescribed an opioid and an oral corticosteroid at the same time, resulting in steroid-induced immunosuppression. Fourth, to address the bias which could arise if opioids or benzodiazepines were prescribed to treat pneumonia symptoms, we repeated our primary analysis excluding prescriptions filled within 10 days prior to index date. Fifth, we carried out analyses focused on the three most commonly used opioids: codeine, hydrocodone, and oxycodone. We grouped hydrocodone and oxycodone together because according to the immunologic literature, neither is immunosuppressive. Finally, as a post-hoc analysis, we repeated the analysis of chronic long-term opioid use applying a more stringent definition, in which use was considered continuous only if there was no more than a 30 day gap between the expected end date of one prescription and the start date of the next. The intention was to identify a group of chronic long-term users who were filling prescriptions on a regular basis, because we hypothesized that if any increased risk were associated with chronic use, it would be most likely to be seen for this group.

Analyses were carried out using SAS version 9.1 (SAS Institute, Incorporated, Cary, North Carolina, United States) and Stata version 9.2 (StataCorp LP, College Station, Texas, United States).

RESULTS

1039 cases of CAP and 2022 controls were included in these analyses. Their median age was 77, and about half were male (Table 2). Among people with CAP, 352 (33.9%) were hospitalized, and 48 (4.6%) died within 30 days of their index date. A greater proportion of cases than controls had comorbid illnesses, particularly chronic lung or heart disease, as well as more severe disease and functional impairment (Table 2).

Hydrocodone was the most commonly dispensed opioid, followed by codeine and oxycodone (Table 1). About 7% of fills were for long-acting opioids. Compared to people using only short-acting agents, people using long-acting opioids had longer duration of use (median 747 versus 91 days) and higher estimated daily doses (median 51.3 versus 10.0 mg in morphine equivalents). Among benzodiazepines, lorazepam was most commonly used, followed by temazepam and diazepam (Appendix Table 2, online). About one-fourth of benzodiazepine dispensings were for long-half-life medications. Among controls, people currently using opioids or benzodiazepines were more likely than nonusers to be female, to smoke, and to have chronic lung disease and functional impairment (Appendix Tables 3 and 4, online).

Among people with pneumonia, 13.9% were current opioid users, compared to 8.0% of controls (adjusted OR 1.38, 95% CI 1.08 to 1.76, compared to nonuse; Table 3). No association was seen for past use. The association was stronger for long-acting than short-acting opioids and for opioids predicted to be immunosuppressive compared to those predicted not to be immunosuppressive (Figure 2A). Pneumonia risk was elevated for current use that began from 5 to 14 days prior to index date (OR 3.24, 95% CI 1.64 to 6.39) and was closer to the null for use begun more than 90 days prior to index date (OR 1.27, 95% CI 0.91 to 1.77). Among chronic users, no pattern was seen for pneumonia risk in relation to estimated daily dose. Compared to nonuse, the adjusted OR for CAP for an EDD of 1 to 19 mg morphine equivalents was 1.05 (95% CI 0.71 to 1.56); for 20 to 49 mg, 2.30 (95% CI 1.10 to 4.83); and for ≥ 50 mg, 1.37 (95% CI 0.64 to 2.92).

Current benzodiazepine use was present in 8.4% of cases and 4.6% of controls, but this difference disappeared after other variables were taken into account (adjusted OR 1.08, 95% CI 0.80 to 1.47, compared to nonuse). There was no interaction between current opioid and benzodiazepine use ($p=0.69$). No increased risk was seen for use of long-half life

benzodiazepines or heavy use (Figure 2B). For use initiated within the past 30 days, the adjusted OR was 0.91 (95% CI 0.44 to 1.92) compared to nonuse.

Similar results were obtained in sensitivity analyses using a stricter definition for “current use”. In these analyses, 7.4% of cases and 3.5% of controls were current opioid users (adjusted OR 1.43, 95% CI 1.00–2.05). A second sensitivity analysis examined whether the elevated risk seen with use of immunosuppressive opioids was due primarily to use of long-half-life medications. The risk of pneumonia in people using short-acting, immunosuppressive opioids (primarily codeine) was elevated compared to nonusers (OR 1.69, 95% CI 1.10 to 2.61), while for short-acting opioids classified as non-immunosuppressive it was 1.17 (95% CI 0.85 to 1.63). The odds ratio for pneumonia associated with current opioid use in people not receiving oral corticosteroids was 1.29 (95% CI 0.98 to 1.71, vs. nonuse) and in analyses excluding prescriptions filled within 10 days prior to the index date it was 1.24 (0.97 to 1.60). In analyses focusing on the three most commonly used opioids, only current use of codeine was associated with higher pneumonia risk compared to nonuse (OR 1.93; 95% CI, 1.22 to 3.06). No increased risk was seen for current use of oxycodone and/or hydrocodone (OR 1.10, 95% CI 0.78 to 1.55, compared to nonuse). Using a stricter definition of chronic long-term opioid use did not alter results substantially; with the stricter definition, the OR for current opioid users who had initiated use at least 90 days prior to index date was 1.41 (95% CI 0.95 to 2.08) compared to nonusers.

DISCUSSION

We observed higher pneumonia risk with current use of prescription opioids in this study of community-dwelling older adults. Risk was highest with recent initiation of use (within 14 days) and with use of long-acting opioids or those classified as immunosuppressive. No association was seen for current benzodiazepine use.

This is the first large epidemiologic study in a general population to examine opioid use and risk of infection. Strengths of the study include that it is population-based, strengthening generalizability, and that pneumonia outcomes were validated through medical record review. We made extensive efforts to account for potential confounders such as comorbid illnesses and functional and cognitive status, which were ascertained from medical records. Information about opioid and benzodiazepine use came from computerized pharmacy data, eliminating recall bias. Our hypotheses about different pneumonia risk with immunosuppressive vs. nonimmunosuppressive opioids have a clear physiologic and mechanistic basis and were developed a priori based on published immunologic studies.^{11, 12, 14–16}

Several limitations of this study should be considered in interpreting these results. First, residual confounding is always a possibility in observational studies. We had limited measures of functional and cognitive impairment, which could have led to bias. Second, we lacked information about the indication for opioid use. Some patients may have been prescribed opioids for a prodromal illness or for early symptoms of pneumonia. We did not have data about the timing of pneumonia onset, so we addressed this problem in our primary analyses by excluding opioid fills that occurred between 1 and 4 days prior to the case’s diagnosis date. In sensitivity analyses, we excluded fills occurring between 1 and 10 days prior to this date, and the adjusted OR decreased from 1.38 to 1.24. It is difficult to know which of these risk estimates is more valid. If opioids have acute immunosuppressive effects, as suggested by studies in animals,^{11, 12, 14–16} and if these effects wane with continuing exposure,⁸ then the 10-day sensitivity analysis may have excluded the very time period in which an elevated risk would be expected to be present. If so, it may underestimate

the association between opioid use and pneumonia. The best solution would be to collect more precise data about the onset of infection in future studies. Third, this study included few opioid users, leading to low power for some comparisons. We cannot provide a definite answer about whether there is a modest but clinically important increase in risk with use of short-acting opioids or with chronic long-term use. Fourth, there could be misclassification of exposure if people took opioids sporadically or took medications not prescribed to them. We did not have information about illicit opioid use. Finally, we studied patients within a single health care system, which could limit generalizability.

Despite these limitations, our findings are important because millions of older adults are exposed to opioids,^{1, 2} and there is a plausible biologic mechanism for increased risk of infection in opioid users. Until now, this question has received little study. One study of nursing home residents with chronic pain examined outcomes of chronic opioid use and did not observe an association with pneumonia,¹⁹ but the number of pneumonia cases was very small. In addition, the study's inclusion criteria may have led to bias, because patients who discontinued opioids were excluded altogether. This group may disproportionately include patients who experienced adverse events. Another study examined infectious complications in patients hospitalized for severe burns.¹⁸ People who developed an infection had received opioids at higher dosages and for longer duration than controls. To our knowledge, no clinical or epidemiologic study has examined infection risk related to opioid use in a general population.

One noteworthy finding in our study is a substantially higher pneumonia risk soon after initiation of opioids (OR 3.24) that was not seen with long-term use (OR 1.27 for ≥ 90 days of use). This pattern is consistent with some prior immunologic studies which suggest that opioid-induced immunosuppression wanes with continuing exposure to opioids. For instance, in one study, natural killer cell activity was suppressed after 4 but not 14 days of exposure to morphine.⁸ The time frame over which opioids' immunosuppressive effects might wane is not clear, and immunologic studies have yielded conflicting results.^{8, 30-32}

Regarding benzodiazepine use, two population-based case-control studies reported conflicting findings: one observed decreased CAP risk with benzodiazepine use (adjusted OR 0.46, 95 % CI 0.23 to 0.94, compared to nonuse),²⁰ while the second found no association.²¹ Reasons for the discrepancy are unclear because the two studies used very similar methods. Both studies assessed medication use from self-report, which may lead to bias, and both defined use as any use in the prior year, which may be less relevant than use shortly before pneumonia onset. Taken together with prior findings, our results suggest that benzodiazepine use is not associated with increased risk of pneumonia.

Further research about prescription opioids and infection risk is urgently needed, particularly because our findings could have major implications for clinical practice. A randomized trial would address concerns about confounding but likely would not be feasible for logistical and ethical reasons.³³ The relatively low incidence of pneumonia (about 3 per 1000 per year in this age group³⁴) would necessitate a large sample size and lengthy follow-up. Observational studies have potential to advance knowledge in this area but will need to address specific methodologic challenges. Future studies should collect detailed information about the timing of pneumonia onset (to address potential reverse causation) and about potential confounding factors including comorbid illnesses. Our prior work suggests that such studies will need to go beyond administrative data to measure comorbidity, because such data may not be adequate to account for confounding in studies of medications and pneumonia risk.^{23, 35, 36}

In conclusion, because millions of older adults are currently exposed to opioids,^{1, 2} and against a backdrop of immunologic studies suggesting that opioids impair immune function, our findings demonstrate the urgent need for additional investigation of the association between opioid use and infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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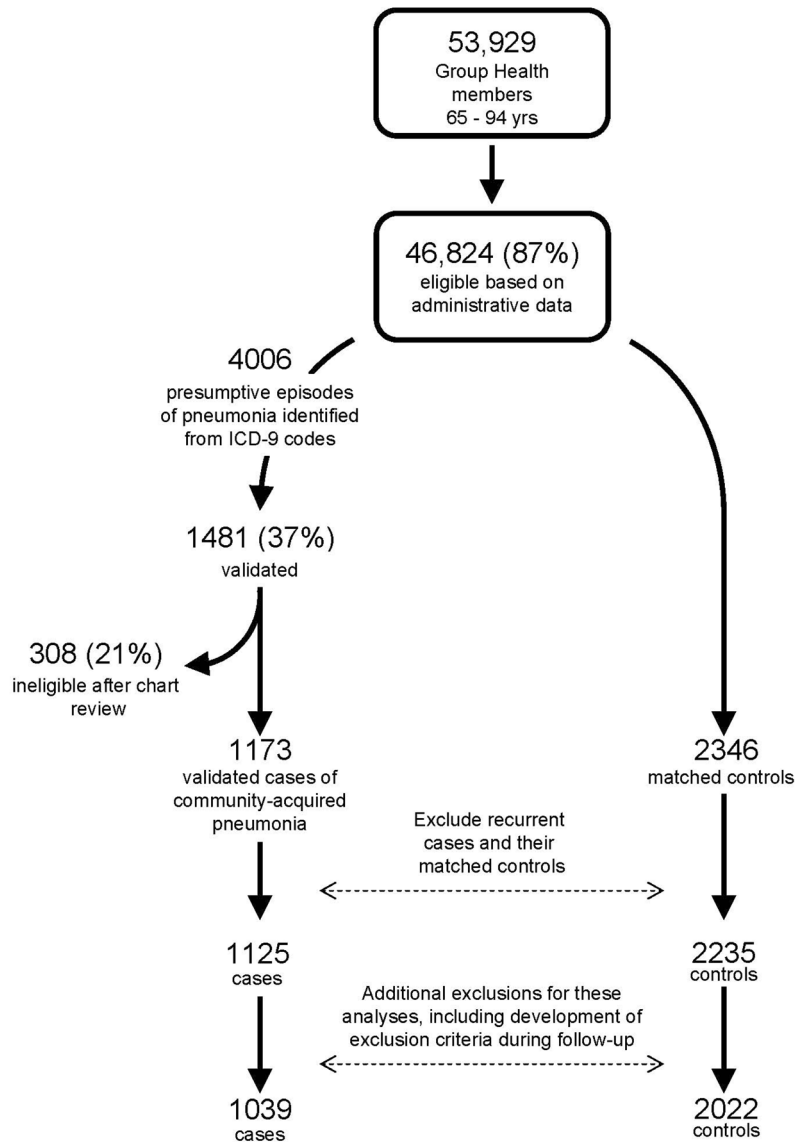


Figure 1.

Selection of cases and controls for inclusion in the study. For this study, we extended the time period during which eligibility was assessed by obtaining additional administrative and pharmacy data to identify exclusion criterion after September 1 of each study year. This process led to the exclusion of an additional 86 cases and 213 controls from the original study. Many of these (61 cases and 17 controls) were people who developed an exclusion criterion during follow-up (after September 1 of their study year). Some additional people were excluded because they were found to have used an immunosuppressive medication during baseline (23 cases, 29 controls) or because the case was discovered to have been hospital-acquired (2 cases and their 4 matched controls). The other 163 controls were dropped because their matched cases had been excluded due to one of the above criteria.

Figure 2A.

Model*	Cases n (%)	Controls n (%)	Odds Ratio	95% Confidence Interval
Current opioid use†	144 (13.9)	161 (8.0)	1.38	(1.08, 1.76)
<i>Stratified by half-life</i>				
Long half-life	18 (1.7)	8 (0.4)	3.43	(1.44, 8.21)
Short half-life	126 (12.1)	152 (7.5)	1.27	(0.98, 1.64)
<i>Stratified by immunosuppressive effects‡</i>				
Immunosuppressive	62 (6.0)	44 (2.2)	1.88	(1.26, 2.79)
Not immunosuppressive	74 (7.1)	101 (5.0)	1.23	(0.89, 1.69)
<i>Stratified by recency of initiation</i>				
5-14 days	17 (1.6)	9 (0.4)	3.24	(1.64, 6.39)
15-30 days	16 (1.5)	27 (1.3)	1.28	(0.72, 2.29)
31 - 90 days	30 (2.9)	43 (2.1)	1.24	(0.78, 1.99)
> 90 days	81 (7.8)	82 (4.1)	1.27	(0.91, 1.77)

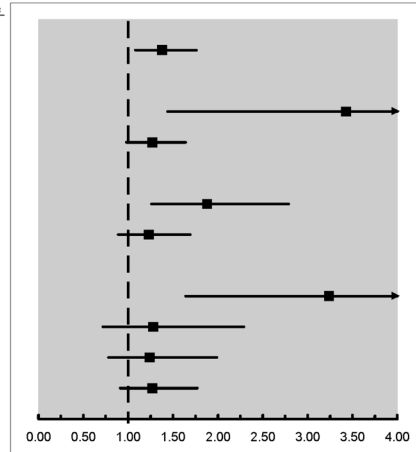


Figure 2B.

Model*	Cases n (%)	Controls n (%)	Odds Ratio	95% Confidence Interval
Current benzodiazepine use†	87 (8.4)	94 (4.6)	1.08	(0.80, 1.47)
<i>Stratified by half-life</i>				
Long half-life	23 (2.2)	26 (1.3)	1.01	(0.60, 1.72)
Short half-life	64 (6.2)	68 (3.4)	1.11	(0.79, 1.56)
<i>Stratified by amount of use in prior year</i>				
Heavy (≥150 TSD‡)	40 (3.8)	46 (2.3)	0.94	(0.60, 1.47)
Light (<150 TSD‡)	47 (4.5)	48 (2.4)	1.22	(0.84, 1.77)
<i>Stratified by recency of initiation</i>				
≤ 30 days	9 (0.9)	11 (0.5)	0.91	(0.44, 1.92)
31 - 90 days	15 (1.4)	19 (0.9)	1.15	(0.61, 2.17)
> 90 days	63 (6.1)	64 (3.2)	1.10	(0.76, 1.59)

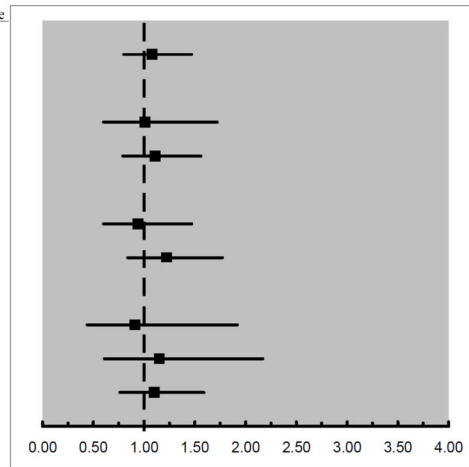


Figure 2.

Figure 2A: Risk estimates for the association between current opioid use and risk of pneumonia, stratified by characteristics of exposure. *Adjusted for matching variables (age, sex, index date), comorbidities, and functional and cognitive status measures. Referent group is non-users. †Current use was defined as receiving ≥ 1 opioid prescription in the 5–60 days prior to index date. ‡According to human and animal studies.^{7–9}

Figure 2B: Risk estimates for the association between current benzodiazepine use and risk of pneumonia, stratified by characteristics of exposure. *Adjusted for matching variables (age, sex, index date), comorbidities, and functional and cognitive status measures. Referent group is non-users. †Current use was defined as receiving ≥ 1 benzodiazepine prescription in the 5–60 days prior to index date. ‡Total standardized doses.

Table 1
Opioid Classification Scheme and Use of Individual Medications by Study Subjects

Medication	Number of prescriptions dispensed*		Half-life	Immunosuppressive [†]	Morphine equivalent dose [‡]
	n	%			
Hydrocodone	1,117	34.2%	Short	No	1.0
Codeine	805	24.6%	Short	Yes	0.15
Oxycodone (short acting)	670	20.5%	Short	No	1.5
Propoxyphene	304	9.3%	Short	Unknown	0.23
Morphine (sustained release)	138	4.2%	Long	Yes	1.0
Oxycodone (controlled release)	65	2.0%	Long	No	1.5
Morphine (immediate release)	45	1.4%	Short	Yes	1.0
Meperidine	44	1.3%	Short	Unknown	0.1
Hydromorphone	27	0.8%	Short	No	4.0
Fentanyl (transdermal)	23	0.7%	Long	Yes	2.4
Tincture of opium	13	0.4%	Unknown	Unknown	10.0
Tramadol	11	0.3%	Short	No	0.10
Methadone	3	0.1%	Long	Yes	3.0
Levorphanol	1	0.0%	Long	Unknown	11.0
Total	3,266	100%			

* Number of prescriptions dispensed between 5–365 days prior to index date for cases and controls.

[†] Based on human and animal studies.^{11, 15, 16, 26}

[‡] Conversion factors are based on information from multiple sources and were arrived at by consensus of several investigators in a prior study of opioid medication use.²⁸ For tincture of opium, the conversion factor is based on information from Thomson Micromedex.²⁷ To use conversion factors, multiply the amount of opioid by the conversion factor to get the amount of morphine. E.g. 200 mg of codeine is equivalent to 200 * 0.15 = 30 mg of morphine, and 20 mg of oxycodone is equivalent to 20 * 1.5 = 30 mg of morphine.

Table 2

Characteristics of Pneumonia Cases and Controls

Characteristic *	Pneumonia cases (N=1,039) n (%) [†]	Controls (N=2,022) n (%) [†]
Median age (IQR), years [‡]	77 (71 – 82)	77 (71 – 82)
Male [‡]	525 (50.5)	1030 (50.9)
Median BMI (IQR), kg/m ² [‡]	26.5 (23.4 – 30.6)	27.3 (24.5 – 30.6)
	(N=736)	(N=1341)
Current smoker	94/1027 (9.2)	101/1972 (5.1)
Asthma	185 (17.8)	158 (7.8)
Chronic obstructive pulmonary disease (COPD)	324 (31.2)	227 (10.4)
Hospitalized for COPD	50 (4.8)	14 (0.7)
Home oxygen use	83 (8.0)	18 (0.9)
Long term steroid use for lung disease	28 (2.7)	6 (0.3)
FEV ₁ measured	166 (16.0)	78 (3.9)
Congestive heart failure (CHF)	192 (18.5)	141 (7.0)
Hospitalized for CHF	33 (3.2)	16 (0.8)
Ejection fraction measured	72 (6.9)	35 (1.7)
Myocardial infarction	126 (12.1)	199 (9.8)
Coronary revascularization	145 (14.0)	224 (11.1)
Stroke	87 (8.4)	140 (6.9)
Swallowing disorder leading to aspiration	13 (1.3)	9 (0.4)
Alcoholism	16 (1.5)	22 (1.1)
Diabetes mellitus	172 (16.6)	300 (14.8)
Dementia	48 (4.6)	68 (3.4)
At least one functional impairment	191 (18.4)	232 (11.5)
Requires assistance bathing	22 (2.1)	15 (0.7)
Requires assistance walking	184 (17.7)	221 (10.9)
Any use of home health services	150 (14.4)	125 (6.2)
Frail [§]	84 (8.1)	58 (2.9)
Bronchodilator use ^{//}	138 (13.3)	51 (2.5)
Furosemide use ^{//}	231 (22.2)	206 (10.2)
Inhaled corticosteroid use ^{//}	244 (23.5)	159 (7.9)
Insulin or oral hypoglycemic use ^{//}	114 (11.0)	188 (9.3)
Oral corticosteroid use ^{//}	262 (25.2)	191 (9.4)
Received pneumococcal vaccine [¶]	951 (91.5)	1846 (91.3)
Received influenza vaccine ^{**}	630 (60.6)	1245 (61.6)
Number of outpatient visits, median (IQR) ^{‡†}	11 (6 – 17)	8 (5 – 14)

Abbreviations: BMI, body mass index; IQR, interquartile range; FEV₁, forced expiratory volume in 1 second.

* All characteristics are defined as of September 1, and the time period of interest is the 2 year baseline period unless otherwise stated.

[†] Results are provided as n (%) unless otherwise stated. Less than 5% of people had missing values for all characteristics except for BMI, which was missing for 29% (303/1039) of cases and 34% (681/2022) of controls.

[‡] Matching variable used in selection of controls.

[§] Ever described as frail by medical personnel (from chart review).

^{//} Defined from computerized pharmacy data as filling at least one prescription for a medication in this class during the 2 year baseline period.

[¶] Any history of receiving pneumococcal vaccine.

^{**} Receipt of the current year's influenza vaccine prior to index date.

^{††} Number of visits in 1-year baseline.

Table 3

Risk of Community-Acquired Pneumonia in Relation to Use of Opioids and Benzodiazepines

	Cases (N=1,039) n (%)	Controls (N=2,022) n (%)	Odds ratio (95% CI)	
			Adjusted for matching variables [†]	Fully adjusted [‡]
Opioid use [*]				
No use	695 (66.9)	1527 (75.5)	1.00 (Ref.)	1.00 (Ref.)
Current use	144 (13.9)	161 (8.0)	1.91 (1.55, 2.36)	1.38 (1.08, 1.76)
Past use	200 (19.2)	334 (16.5)	1.31 (1.12, 1.54)	1.06 (0.88, 1.27)
Benzodiazepine use [*]				
No use	892 (85.9)	1796 (88.8)	1.00 (Ref.)	1.00 (Ref.)
Current use	87 (8.4)	94 (4.6)	1.63 (1.26, 2.11)	1.08 (0.80, 1.47)
Past use	60 (5.8)	132 (6.5)	0.82 (0.63, 1.07)	0.62 (0.46, 0.85)

Abbreviations: CAP, community-acquired pneumonia; CHF, congestive heart failure; CI, confidence interval; FEV₁, forced expiratory volume in 1 second.

^{*} Current use is defined as having ≥ 1 fill for a medication in the specified class within 5–60 days prior to the case's pneumonia diagnosis date. Non-users had no fills from 5–365 days prior to index date. Past users had ≥ 1 fill from 61–365 days prior to index date but none in the 5–60 days prior to index date.

[†] Adjusted only for age, sex, and index date.

[‡] Adjusted for matching variables above and for asthma, chronic obstructive pulmonary disease (COPD) and history of COPD hospitalization, use of home oxygen, long-term steroid use for lung disease, FEV₁ measured, congestive heart failure (CHF) and history of CHF hospitalization, ejection fraction measured, stroke, dementia, need for assistance with ambulation or bathing, number of outpatient visits, and use of the following medications: inhaled bronchodilators, inhaled corticosteroids, oral corticosteroids, or furosemide