Mortality and concurrent use of opioids and hypnotics in older patients: A retrospective cohort study

Wayne A. Ray¹*, Cecilia P. Chung², Katherine T. Murray³, Beth A. Malow⁴, James R. Daugherty¹, C. Michael Stein³

¹ Department of Health Policy, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America, ² Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America, ³ Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America, ⁴ Department of Neurology, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America

* wayne.ray@vumc.org

Abstract

Background
Benzodiazepine hypnotics and the related nonbenzodiazepine hypnotics (z-drugs) are among the most frequently prescribed medications for older adults. Both can depress respiration, which could have fatal cardiorespiratory effects, particularly among patients with concurrent opioid use. Trazodone, frequently prescribed in low doses for insomnia, has minimal respiratory effects, and, consequently, may be a safer hypnotic for older patients. Thus, for patients beginning treatment with benzodiazepine hypnotics or z-drugs, we compared deaths during periods of current hypnotic use, without or with concurrent opioids, to those for comparable patients receiving trazodone in doses up to 100 mg.

Methods and findings
The retrospective cohort study in the United States included 400,924 Medicare beneficiaries 65 years of age or older without severe illness or evidence of substance use disorder initiating study hypnotic therapy from January 2014 through September 2015. Study endpoints were out-of-hospital (primary) and total mortality. Hazard ratios (HRs) were adjusted for demographic characteristics, psychiatric and neurologic disorders, cardiovascular and renal conditions, respiratory diseases, pain-related diagnoses and medications, measures of frailty, and medical care utilization in a time-dependent propensity score–stratified analysis. Patients without concurrent opioids had 32,388 person-years of current use, 260 (8.0/1,000 person-years) out-of-hospital and 418 (12.9/1,000) total deaths for benzodiazepines; 26,497 person-years, 150 (5.7/1,000) out-of-hospital and 227 (8.6/1,000) total deaths for z-drugs; and 16,177 person-years, 156 (9.6/1,000) out-of-hospital and 256 (15.8/1,000) total deaths for trazodone. Out-of-hospital and total mortality for benzodiazepines (respective HRs: 0.99 [95% confidence interval, 0.81 to 1.22, p = 0.954] and 0.95 [0.82 to 1.14, p = 0.513]) and z-drugs (HRs: 0.96 [0.76 to 1.23], p = 0.767 and 0.87 [0.72 to 1.05], p = 0.153).
did not differ significantly from that for trazodone. Patients with concurrent opioids had 4,278 person-years of current use, 90 (21.0/1,000) out-of-hospital and 127 (29.7/1,000) total deaths for benzodiazepines; 3,541 person-years, 40 (11.3/1,000) out-of-hospital and 64 (18.1/1,000) total deaths for z-drugs; and 2,347 person-years, 19 (8.1/1,000) out-of-hospital and 36 (15.3/1,000) total deaths for trazodone. Out-of-hospital and total mortality for benzodiazepines (HRs: 3.02 [1.83 to 4.97], \( p < 0.001 \) and 2.21 [1.52 to 3.20], \( p < 0.001 \)) and z-drugs (HRs: 1.98 [1.14 to 3.44], \( p = 0.015 \) and 1.65 [1.09 to 2.49], \( p = 0.018 \)) were significantly increased relative to trazodone; findings were similar with exclusion of overdose deaths or restriction to those with cardiovascular causes. Limitations included composition of the study cohort and potential confounding by unmeasured variables.

## Conclusions

In US Medicare beneficiaries 65 years of age or older without concurrent opioids who initiated treatment with benzodiazepine hypnotics, z-drugs, or low-dose trazodone, study hypnotics were not associated with mortality. With concurrent opioids, benzodiazepines and z-drugs were associated with increased out-of-hospital and total mortality. These findings indicate that the dangers of benzodiazepine–opioid coadministration go beyond the documented association with overdose death and suggest that in combination with opioids, the z-drugs may be more hazardous than previously thought.

## Author summary

### Why was this study done?

- Benzodiazepines and the related z-drugs are sleep medications commonly prescribed for persons 65 years of age or older.
- Both can interfere with breathing, which, in turn, may cause irregular heartbeat and deaths.
- Opioid painkillers, often used with sleep medications, also interfere with breathing and thus could increase the likelihood of deaths with benzodiazepines or z-drugs.
- Trazodone, an antidepressant that in low doses often is prescribed for insomnia, has not been found to affect breathing and thus may be safer for older patients, particularly for those also taking opioids.

### What did the researchers do and find?

- We identified 400,924 persons in the US Medicare program 65 or older who began treatment with benzodiazepine, z-drug, or trazodone sleep medications.
- For patients without and with opioid use, we compared the rate of out-of-hospital deaths—often related to heart problems—and total mortality during treatment with benzodiazepines and z-drugs to that for trazodone.
For patients with opioid exposure, benzodiazepines were associated with respective 302% and 221% increases in out-of-hospital and total mortality, and z-drugs were associated with respective 98% and 65% increases in out-of-hospital and total mortality.

What do these findings mean?

- In older populations, the risks of concurrent benzodiazepine–opioid exposure go beyond the known increased likelihood of overdose, suggesting that greater efforts are needed to prevent use of this medication combination.
- Patients and clinicians should be aware that in combination with opioids, the z-drugs, thought to be relatively safe, may increase the risk of death.

Introduction

Hypnotics are among the most frequently prescribed medications for older adults [1–3]. The 3 most commonly prescribed medications for insomnia in the US are the benzodiazepines, the z-drugs, and low-dose trazodone [4,5]. Benzodiazepines stimulate γ-aminobutyric acid type A (GABA-A) receptors, the major inhibitory neurotransmitter in the central nervous system [6]. The z-drugs (zolpidem and related nonbenzodiazepine hypnotics) are GABA-A agonists that are more selective for the α1 subtype receptors thought to mediate hypnotic effects [7] and thus hypothesized to reduce the risk of dependence, psychomotor impairment, and injuries reported for benzodiazepines [6,8–10]. Trazodone, an antidepressant without GABA activity [4,11–13], in low doses is often prescribed for insomnia [4,5], although it is not labeled as a hypnotic and guidelines generally only recommend use for insomnia associated with a mood disorder [14].

Although the primary concern with benzodiazepines and z-drugs has been the risk of dependence and injuries [6,8–10], these drugs also have potentially fatal respiratory effects. Benzodiazepines depress respiration [7,15,16] and thus can exacerbate sleep-disordered breathing [17,18], which, in turn, can trigger life-threatening cardiac arrhythmias [19–21]. In overdose, benzodiazepines can cause airway obstruction or respiratory failure [22]. The z-drugs also impair respiration, although to a lesser degree than for benzodiazepines [18,23]. In contrast, respiratory impairment has not been observed for trazodone [24,25], although it infrequently has serious adverse cardiovascular effects [26,27].

The frequent use of opioid analgesics with both benzodiazepines and z-drugs [28–31] could increase the risk of adverse cardiorespiratory effects. Opioids profoundly depress respiration [32–34], cause sleep-disordered breathing [34,35], increase the likelihood of airway obstruction and respiratory failure [36], and are associated with increased risk of out-of-hospital cardiovascular death [37]. Although the Food and Drug Administration (FDA) requires a boxed warning (“black box”) concerning coadministration of benzodiazepines and opioids because of greater likelihood of overdose death [28], such deaths are relatively uncommon in older populations [38]. However, an increased risk of cardiovascular deaths, the most common cause of death for persons 65 years of age or older [38], with concurrent use of benzodiazepines or z-drugs with opioids would have major public health implications.

Thus, to better define the relative safety of commonly prescribed hypnotics, both without and with concurrent opioids, we compared mortality in US Medicare enrollees 65 years of age...
or older without severe illnesses initiating treatment with benzodiazepine hypnotics, z-drugs, or low-dose trazodone.

**Methods**

**Design**

We conducted a retrospective cohort study using the computerized files of the US Medicare program, which provided an efficient means to identify the cohort and obtain study data [39]. The protocol is shown in S1 Protocol. The study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (S1 Checklist). The study was approved by the Vanderbilt Medical Center Ethics Committee.

**Cohort**

**Medicare data.** Medicare provides healthcare insurance for nearly all US citizens 65 years of age or older [40]. All Medicare beneficiaries have coverage for inpatient/skilled nursing facility stays (Part A) and also may elect coverage for outpatient services (Part B) and prescription medications (Part D). Enrollees can choose either a fee-for-service plan or Medicare Advantage (Part C), a managed care model. To ensure completeness of data, our study was restricted to enrollees with Parts A, B, and D who had fee-for-service coverage, because Medicare Advantage healthcare encounter data were considered less reliable during the study years [40]. In 2019, there were 53 million Medicare enrollees 65 years of age or older, of whom 26 million had fee-for-service Parts A, B, and D [41].

The Medicare enrollment file records periods of enrollment for each part of Medicare. It identifies deaths for >95% of persons 65 and older in the US [40], which have been linked to the National Death Index (NDI). Other files include medical care encounters for pharmacy, hospital, outpatient, and nursing home services. The data reside in the Center for Medicare & Medicaid Services (CMS) Chronic Condition Warehouse (Section C.1 in S1 Appendix) and were accessed through the Virtual Research Data Center (VRDC), a cloud-based repository of de-identified Medicare files [42]. In accordance with CMS policy, no table cells with fewer than 11 patients were reported. The study was approved by the Vanderbilt University Medical Center Institutional Review Board, with waiver of informed consent.

**Study medications.** Study hypnotics (Table A in S1 Appendix) included selected benzodiazepines, z-drugs, and trazodone in doses up to 100 mg (recommended for hypnotic use, but lower than doses for treatment of mood disorders) [43]. The study benzodiazepines were those with a labeled hypnotic indication (estazolam, flurazepam, quazepam, temazepam, and triazolam), as well as alprazolam, clonazepam, and lorazepam, which have similar pharmacodynamic properties, are prescribed for insomnia and are included in guidelines for hypnotics [6,10]. Patients for whom the prescribed regimen was inconsistent with hypnotic use (more than 1 tablet/capsule per day) or for whom there was evidence of an alternative indication for benzodiazepines or trazodone (diagnosis in the past 90 days indicating panic disorder, anxiety/post-traumatic stress disorder, neurologic indications for benzodiazepines, major depression, or bipolar disorder) were excluded from the cohort (Section A in S1 Appendix).

The study opioids (Table B in S1 Appendix) excluded parenteral opioids (infrequently prescribed for outpatients) and preparations specifically formulated for cough or diarrhea. Opioids were classified as short or long acting, and dose equivalents were calculated in morphine milligram equivalents (MME) according to guidelines for chronic opioid therapy for non-cancer pain [43].

**Cohort eligibility.** The cohort (Table C in S1 Appendix) consisted of Medicare beneficiaries 65 years of age or older who filled a study hypnotic prescription between January 1, 2014
and September 29, 2015. They had to have complete demographic information and in the past year have enrollment in Medicare Parts A, B, and D but not Part C, thus limiting the cohort to beneficiaries with fee-for-service coverage. To assure regular contact with medical care, cohort members had to have at least 1 outpatient visit and 1 filled prescription (other than the study hypnotic) in the prior year.

The cohort was restricted to new users of hypnotic medications, which permits better ascertainment of deaths early in therapy in susceptible patients and assures baseline covariates are not influenced by the study hypnotics [44]. Thus, cohort members could not have filled a prescription in the past year for any study hypnotic (other than a single day of supply, often peri-procedural), non-study benzodiazepine, or non-study hypnotic (Table C in S1 Appendix).

Hypnotics and opioids often are initiated for patients with unstable or life-threatening illness, which increases the likelihood of difficult-to-control confounding [6,45] and reduces the capacity to detect drug-associated mortality [37]. Thus, the cohort excluded patients in nursing homes, with hospice care, with recent hospitalizations indicating unstable illness, and with active cancer or other life-threatening disease (Table D in S1 Appendix). To assess the effects of therapeutic study drug use, patients with diagnosed substance use disorder or use of buprenorphine, most commonly prescribed as opioid replacement therapy, were excluded.

**Follow-up.** Cohort follow-up began on the day following the fill date for the first study hypnotic prescription. Follow-up ended with prescription of a hypnotic medication from a different class, a non-study benzodiazepine or trazodone >100 mg as well as with loss of full fee-for-service (Parts A, B, and D and no C) Medicare enrollment, nursing home or hospice entry, hospital stay >30 days, substance use disorder diagnosis, September 30, 2015, or death. Patients who left the cohort could not reenter. Because the postulated mechanisms by which study medications affect mortality require presence of the drug [17], follow-up and analysis were restricted to current hypnotic use (Fig A in S1 Appendix): The prescription fill through end of dispensed days of supply (offset 1 day to account for probable nocturnal hypnotic use).

Opioids could be started or stopped at any time during follow-up. Thus, both current use and its characteristics (start past 90 days, long-acting drug, dose) were determined for each person-day of follow-up. A single patient could have person-time both with and without concurrent opioids (Fig 1); however, because there was no overlap and the endpoint occurred only once, statistical independence assumptions were satisfied [24].

**Endpoints**

Deaths were identified from the Medicare Master Beneficiary Summary File, and the underlying cause of death (Table E in S1 Appendix) came from the linked NDI. The small number of beneficiaries with a Medicare date of death but no linked NDI record (1.4%) were considered deaths of unknown cause.

The primary endpoint included all out-of-hospital deaths for several reasons. First, in patients without severe illness, a substantial proportion of deaths are plausibly related to cardiac arrhythmias. In a previous investigation of opioid use for non-cancer chronic pain with medical record review [37,46], 73% of out-of-hospital deaths were sudden unexpected deaths consistent with a cardiac arrhythmia. Second, both our experience [37] and that of others [47] suggests that US death certificates under-ascertain cardiovascular deaths, particularly for out-of-hospital deaths in older patients for whom postmortem investigations may be limited [48]. Third, benzodiazepines and opioids, particularly in overdose, have respiratory effects—decreased ventilation, airway obstruction, and respiratory failure [22,36]—that can lead to sudden unexpected death. A sensitivity analysis restricted deaths to those with a cardiovascular cause.
Analysis

Covariates.Study comparisons controlled for 105 covariates plausibly associated with both risk of death and the use of specific hypnotics or opioids (Section G and Table F in S1 Appendix). The covariates, defined from medical care encounters in the year preceding cohort.
entry, were based on our previous studies of out-of-hospital death [37,46], standard measures of comorbidity [49,50], and indicators of frailty [51]. They included demographic characteristics (including self-reported race, indicator of genetic factors potentially influencing drug metabolism), psychiatric and neurologic disorders, cardiovascular and renal conditions, respiratory diseases, pain-related diagnoses and medications, measures of frailty, and medical care utilization. Because comorbidity could change during follow-up, covariate values (other than opioid characteristics) were updated on the date of each hypnotic prescription fill.

**Propensity score.** All covariates (other than opioid characteristics) were controlled for by stratifying the analysis according to deciles (distribution in trazodone group) of the appropriate pairwise propensity score, the probability of trazodone use, given the covariates (Section H in S1 Appendix) [52,53]. Because the covariates were updated at the time of each hypnotic prescription fill during follow-up, the propensity scores were time dependent [54]. After weighting, the distributions of covariates differed little between treatment groups (Table G in S1 Appendix).

**Statistical analysis.** The adjusted relative risk of death was estimated with hazard ratios (HRs) from a stratified time-dependent proportional hazards regression (Section I in S1 Appendix) [55]. The timescale was cumulative days of current hypnotic use, creating risk sets of patients with the same treatment duration. For patients with opioid use, the model included terms for opioid current use and its characteristics. Because opioid prescriptions could be filled at any time during follow-up, these variables were updated on a daily basis. Statistical significance was defined as 95% Wald confidence intervals that excluded 1, with \( p \)-values calculated accordingly. Because the study comparisons were planned, \( p \)-values were not adjusted for multiple comparisons. All analyses were done with SAS version 9.4.

**Sensitivity analyses.** Sensitivity analyses were performed that examined groups of particular interest or used an alternative statistical analysis. The former included restriction of endpoints to non-overdose deaths or deaths from cardiovascular causes and exclusion of possible non-hypnotic benzodiazepine use by requiring the benzodiazepine to be labeled as a hypnotic or the patient to have a recent insomnia diagnosis. The alternative statistical analyses (Section I in S1 Appendix) accounted for geographic region (assessed region both as clustering factor and confounder), fixed all covariates at baseline except for opioid use and characteristics (guards against causal pathway confounding), had time-dependent propensity score weights based on all covariates (residual confounding), and used baseline pairwise propensity score matching with only opioid covariates time dependent (causal pathway and residual confounding).

**Results**

**Characteristics of cohort at baseline**

**Entire cohort.** There were 646,226 new users of study hypnotic medications 65 years of age or older with adequate Medicare data, of whom 400,924 qualified for the cohort (Fig 1). The most frequently prescribed individual benzodiazepines were alprazolam (39.8% of patients receiving benzodiazepine), lorazepam (27.7%), and temazepam (17.9%); zolpidem was the most frequently prescribed z-drug (91.1%). Cohort members had a mean age of 75.5 (std 7.3) years, and 65.9% were female.

**No concurrent opioid.** At baseline, 349,105 cohort members did not have concurrent opioid use, including 152,711 new users of benzodiazepines, 134,359 of z-drugs, and 62,035 of trazodone. Comorbidity levels in the past year were consistently higher for the trazodone group than for z-drugs (Table 1, Table F in S1 Appendix). The patients beginning trazodone use were more likely to have Medicaid enrollment (22.4% versus 14.7%), mood disorders
Table 1. Baseline cohort characteristics* according to concurrent opioid use.

|                        | No concurrent opioid use | Concurrent opioid use |
|------------------------|--------------------------|-----------------------|
|                        | Benzo-diazepines  | z-Drugs   | Trazodone  | Benzo-diazepines | z-Drugs   | Trazodone  |
| N                      | 152,711      | 134,359      | 62,035    | 21,805         | 20,522      | 9,492        |
| Dose, mean, mg      | 8.9          | 7.4          | 52.2      | 10.0           | 7.6          | 54.9         |
| Age, mean (std)      | 76.1 (7.6)   | 74.3 (6.8)   | 76.6 (7.8) | 75.6 (7.6)    | 74.0 (6.8)   | 75.6 (7.7)   |
| Female                | 70.3%        | 60.4%        | 67.5%     | 68.8%          | 60.2%        | 67.2%        |
| White race           | 87.2%        | 84.9%        | 82.6%     | 85.5%          | 84.4%        | 81.5%        |
| Entered cohort in 2014| 57.6%        | 59.0%        | 54.1%     | 58.3%          | 59.4%        | 56.5%        |
| Medicaid              | 15.7%        | 14.7%        | 22.4%     | 25.5%          | 23.5%        | 35.3%        |
| Psychiatric/neurologic |            |              |           |                |              |              |
| Mood disorder         | 13.5%        | 10.1%        | 19.4%     | 16.6%          | 13.6%        | 23.0%        |
| Anxiety, panic disorder, or PTSD | 8.7% | 4.3% | 5.8% | 8.6% | 5.2% | 6.9% |
| Alzheimer and other dementias | 8.3% | 3.8% | 13.4% | 6.3% | 3.9% | 8.7% |
| Selective serotonin reuptake inhibitors | 19.3% | 14.1% | 20.0% | 20.3% | 17.5% | 22.8% |
| Other antidepressant  | 10.4%        | 9.6%         | 14.2%     | 17.2%          | 16.1%        | 22.2%        |
| Cardiovascular/renal  |              |              |           |                |              |              |
| Myocardial infarction | 3.9%         | 3.5%         | 4.1%      | 4.9%           | 5.1%         | 5.3%         |
| Heart failure         | 8.8%         | 7.6%         | 9.6%      | 12.2%          | 10.4%        | 13.2%        |
| Diabetes              | 30.8%        | 29.4%        | 33.0%     | 36.5%          | 35.8%        | 38.1%        |
| Smoking and smoking-related disorders | 9.4% | 9.4% | 11.8% | 14.7% | 16.0% | 19.0% |
| Chronic kidney disease| 10.5%        | 9.0%         | 12.6%     | 13.5%          | 12.1%        | 16.0%        |
| Beta-blockers         | 39.9%        | 34.6%        | 38.9%     | 42.0%          | 38.2%        | 44.0%        |
| Diuretics, loop       | 12.8%        | 10.5%        | 14.7%     | 20.9%          | 17.3%        | 23.5%        |
| Hypoglycemics, insulin| 4.7%         | 4.5%         | 6.5%      | 7.6%           | 7.2%         | 9.5%         |
| Hypoglycemics, metformin| 13.5% | 14.0% | 16.6% | 16.7% | 17.1% | 18.0% |
| Respiratory           |              |              |           |                |              |              |
| Chronic obstructive pulmonary disease | 11.7% | 10.0% | 12.8% | 18.2% | 16.2% | 21.4% |
| Home oxygen           | 4.3%         | 4.0%         | 5.0%      | 7.2%           | 6.1%         | 8.6%         |
| Beta-agonists         | 11.5%        | 11.2%        | 12.7%     | 16.0%          | 15.6%        | 19.0%        |
| Pain                  |              |              |           |                |              |              |
| Neuropathic pain      | 21.2%        | 21.5%        | 20.7%     | 36.7%          | 35.5%        | 36.8%        |
| Headache, including migraine | 10.2% | 8.9% | 10.2% | 12.6% | 11.6% | 12.5% |
| Cyclobenzaprine/other skeletal muscle relaxant | 6.3% | 6.5% | 6.8% | 15.9% | 16.3% | 18.2% |
| Gabapentinoids/carbamazepine | 9.8% | 9.5% | 11.6% | 23.6% | 22.8% | 28.8% |
| Frailty               |              |              |           |                |              |              |
| Unintentional fall (not vigorous activity) | 7.0% | 5.4% | 9.4% | 10.5% | 9.2% | 12.3% |
| Wheelchair, hospital bed, or difficulty transfers | 2.3% | 1.8% | 3.3% | 4.8% | 4.0% | 6.1% |
| Malnutrition1         | 7.4%         | 6.1%         | 8.8%      | 9.1%           | 7.6%         | 10.7%        |
| Medical care in past 90 days |          |              |           |                |              |              |
| Inpatient discharge   | 1.8%         | 2.2%         | 2.3%      | 3.1%           | 4.6%         | 3.7%         |
| Emergency department visit | 9.9% | 7.4% | 10.9% | 15.1% | 13.0% | 15.4% |
| Home health visit     | 4.3%         | 3.0%         | 5.6%      | 7.8%           | 6.7%         | 9.1%         |
| Opioid characteristics |              |              |           |                |              |              |
| Long acting           | 0.0%         | 0.0%         | 0.0%      | 4.8%           | 4.3%         | 5.7%         |
| Started past 90 days  | 0.0%         | 0.0%         | 0.0%      | 25.1%          | 27.1%        | 13.9%        |

(Continued)
(19.7% versus 10.3%), dementia (13.5% versus 3.9%), chronic kidney disease (12.6% versus 9.1%), chronic obstructive pulmonary disease (13.1% versus 10.1%), history of falls (9.2% versus 5.5%), and malnutrition or feeding problems (8.9% versus 6.2%). The comorbidity levels for patients initiating trazodone were also higher than those for benzodiazepines, although the differences were less pronounced.

Concurrent opioid. At baseline, 51,819 cohort members had concurrent opioid use, 12.9% of the cohort. These included 21,805 new users of benzodiazepines, 20,522 of z-drugs, and 9,492 of trazodone. The covariates indicated greater comorbidity for the trazodone group than for the z-drugs (Table 1, Table F in S1 Appendix) as well as similar, although less pronounced, differences between patients receiving trazodone and benzodiazepines. Those with use of trazodone were less likely to have started the opioid within the past 90 days but were more likely to receive a long-acting drug and higher doses.

Deaths during follow-up

Entire cohort. During 85,277 person-years of follow-up, there were 1,128 deaths (13.2/1,000 person-years), of which 715 (8.4/1,000) were out-of-hospital, and 413 (4.8/1,000) were in hospital. The underlying causes of study deaths were cardiovascular (59.0% of deaths), respiratory (10.2%), neurologic (6.9%), injuries (6.8%), cancer (4.3%), and other causes (12.8%).

No concurrent opioid. During 75,061 person-years of follow-up without concurrent opioid use, there were 32,388 person-years and 260 out-of-hospital deaths for benzodiazepines (8.0/1,000), 26,497 person-years and 150 deaths for z-drugs (5.7/1,000), and 16,177 person-years and 156 deaths (9.6/1,000) for trazodone (Table 2). After adjustment for covariates, the risk of out-of-hospital death for benzodiazepines (Fig 2, HR = 0.99 [0.81 to 1.23], \( p = 0.954 \)) and z-drugs (HR = 0.96 [0.76 to 1.23], \( p = 0.767 \)) did not differ significantly from that for trazodone, nor were there significant differences in the adjusted risk of total study mortality (benzodiazepines, HR = 0.95 [0.80 to 1.12], \( p = 0.513 \); z-drugs, HR = 0.87 [0.72 to 1.05], \( p = 0.153 \)). When the benzodiazepines were compared with the z-drugs (Table H in S1 Appendix), there were no significant differences for out-of-hospital or total mortality.

Concurrent opioid. During 10,166 person-years of follow-up with concurrent opioid use, there were 4,278 person-years and 90 out-of-hospital deaths for benzodiazepines (21.0/1,000), 3,541 person-years and 40 deaths for z-drugs (11.3/1,000), and 2,347 person-years and 19 deaths (8.1/1,000) for trazodone (Table 2). When compared with trazodone (Fig 2), the risk of out-of-hospital death was increased for both benzodiazepines (HR = 3.02 [1.83 to 4.97], \( p < 0.001 \)) and z-drugs (HR = 1.98 [1.14 to 3.44], \( p = 0.015 \)). The increased risk remained
When the out-of-hospital deaths were restricted to those with cardiovascular causes (Table 3), the adjusted risk of total mortality for both benzodiazepines (HR = 2.21 [1.52 to 3.20], \( p < 0.001 \)) and z-drugs (HR = 1.65 [1.09 to 2.50], \( p = 0.018 \)) was greater than that for trazodone. When the benzodiazepines were compared with the z-drugs (Table H in S1 Appendix), there were no significant differences for out-of-hospital or total mortality.

### Sensitivity analyses

HR estimates were little changed with the exclusion of drug overdose deaths, restriction of deaths to those with cardiovascular causes, or limiting benzodiazepines to patients who started a drug with a hypnotic label or had an insomnia diagnosis prior to cohort entry (Table 3). The HRs estimated with alternative statistical methods did not differ materially from those of the primary analysis.

### Table 2. Unadjusted incidence of death (per 1,000 person-years) during follow-up according to study hypnotic and concurrent opioid use.

|                      | Benzodiazepine | z-drugs | Trazodone |
|----------------------|----------------|---------|-----------|
| **No concurrent opioid use** |                |         |           |
| Person-years         | 32,388         | 26,497  | 16,177    |
| Deaths               | 260            | 150     | 156       |
| Rate (95% CI)        | 8.0 (7.1 to 9.0)| 5.7 (4.8 to 6.6)| 9.6 (8.1 to 11.2)|
| Out of hospital      |                |         |           |
| In hospital          | 158            | 77      | 100       |
| All                  | 418            | 227     | 256       |
| Rate (95% CI)        | 4.9 (4.1 to 5.6)| 2.9 (2.3 to 3.6)| 6.2 (5.0 to 7.4)|
| **Concurrent opioid use** | 4,278          | 3,541   | 2,347     |
| Person-years         | 90             | 40      | 19        |
| Deaths               | 21.0 (16.7 to 25.4)| 11.3 (7.8 to 14.8)| 8.1 (4.5 to 11.7)|
| Rate (95% CI)        | 8.6 (5.9 to 11.4)| 6.8 (4.1 to 9.5)| 7.2 (3.8 to 10.7)|
| Out of hospital      | 37             | 24      | 17        |
| In hospital          |                |         |           |
| All                  | 127            | 64      | 36        |
| Rate (95% CI)        | 29.7 (24.5 to 34.8)| 18.1 (13.6 to 22.5)| 15.3 (10.3 to 20.3)|

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**Fig 2.** Adjusted HRs for benzodiazepines and z-drugs vs. trazodone for out-of-hospital and total mortality, according to concurrent opioid use. The bars indicate the 95% confidence intervals for the HRs. The adjusted HRs for the comparisons of benzodiazepines vs. z-drugs are shown in Table H in S1 Appendix. HR, hazard ratio.

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Table 3. Sensitivity analyses for benzodiazepines and z-drugs vs. trazodone, according to concurrent opioid use.

|                      | No concurrent opioid |                      | Concurrent opioid |                      |
|----------------------|----------------------|----------------------|-------------------|----------------------|
|                      | Benzodiazepines      | z-drugs              | Benzodiazepines   | z-drugs              |
|                      | HR (95% CI)          | p-value              | HR (95% CI)       | p-value              |
| Primary analysis     |                      |                      |                   |                      |
| Out-of-hospital deaths | 0.99 (0.81 to 1.22)  | 0.954                | 0.96 (0.76 to 1.23) | 0.767                |
|                      |                      |                      | 3.02 (1.83 to 4.97) | <0.001               |
|                      |                      |                      |                   | 1.98 (1.14 to 3.44)  | 0.015                |
| All deaths           | 0.95 (0.80 to 1.12)  | 0.513                | 0.87 (0.72 to 1.05) | 0.153                |
|                      |                      |                      | 2.21 (1.52 to 3.20) | <0.001               |
|                      |                      |                      |                   | 1.65 (1.09 to 2.49)  | 0.018                |
| (a) Subgroups of interest |                      |                      |                   |                      |
| Overdose deaths excluded |                      |                      |                   |                      |
| Out-of-hospital deaths | 1.00 (0.81 to 1.23)  | 0.977                | 0.96 (0.75 to 1.22) | 0.738                |
|                      |                      |                      | 2.98 (1.81 to 4.91) | <0.001               |
|                      |                      |                      |                   | 1.99 (1.14 to 3.45)  | 0.015                |
| All deaths           | 0.95 (0.81 to 1.12)  | 0.527                | 0.87 (0.72 to 1.05) | 0.144                |
|                      |                      |                      | 2.19 (1.51 to 3.18) | <0.001               |
|                      |                      |                      |                   | 1.65 (1.09 to 2.49)  | 0.017                |
| Cardiovascular deaths only |                      |                      |                   |                      |
| Out-of-hospital deaths | 0.99 (0.77 to 1.28)  | 0.948                | 0.94 (0.70 to 1.26) | 0.660                |
|                      |                      |                      | 3.41 (1.79 to 6.51) | <0.001               |
|                      |                      |                      |                   | 2.65 (1.32 to 5.30)  | 0.006                |
| All deaths           | 0.92 (0.74 to 1.14)  | 0.453                | 0.83 (0.65 to 1.07) | 0.153                |
|                      |                      |                      | 2.24 (1.38 to 3.63) | 0.0012               |
|                      |                      |                      |                   | 1.68 (0.98 to 2.88)  | 0.059                |
| Benzodiazepines hypnotic label or sleep problem diagnosis |                      |                      |                   |                      |
| Out-of-hospital deaths | 0.85 (0.66 to 1.10)  | 0.223                |                   |                      |
|                      |                      |                      | 2.67 (1.54 to 4.64) | <0.001               |
| All deaths           | 0.84 (0.69 to 1.03)  | 0.089                |                   |                      |
|                      |                      |                      | 1.85 (1.20 to 2.85) | 0.0050               |
| (b) Alternative statistical analysis* |                      |                      |                   |                      |
| Clustering by region: variance adjustment |                      |                      |                   |                      |
| Out-of-hospital deaths | 0.99 (0.80 to 1.24)  | 0.960                | 0.96 (0.75 to 1.23) | 0.740                |
|                      |                      |                      | 3.02 (1.83 to 4.99) | <0.001               |
|                      |                      |                      |                   | 1.99 (1.14 to 3.46)  | 0.015                |
| All deaths           | 0.95 (0.80 to 1.12)  | 0.529                | 0.87 (0.71 to 1.06) | 0.157                |
|                      |                      |                      | 2.21 (1.52 to 3.21) | <0.001               |
|                      |                      |                      |                   | 1.65 (1.09 to 2.50)  | 0.018                |
| Cluster by region: control for and variance adjustment |                      |                      |                   |                      |
| Out-of-hospital deaths | 0.99 (0.80 to 1.24)  | 0.959                | 0.96 (0.75 to 1.23) | 0.740                |
|                      |                      |                      | 3.02 (1.83 to 4.99) | <0.001               |
|                      |                      |                      |                   | 1.99 (1.14 to 3.46)  | 0.015                |
| All deaths           | 0.95 (0.80 to 1.12)  | 0.528                | 0.87 (0.71 to 1.06) | 0.158                |
|                      |                      |                      | 2.21 (1.52 to 3.21) | <0.001               |
|                      |                      |                      |                   | 1.65 (1.09 to 2.50)  | 0.018                |
| Covariates fixed at baseline |                      |                      |                   |                      |
| Out-of-hospital deaths | 0.93 (0.76 to 1.15)  | 0.520                | 0.94 (0.73 to 1.20) | 0.590                |
|                      |                      |                      | 2.81 (1.71 to 4.63) | <0.001               |
|                      |                      |                      |                   | 1.97 (1.14 to 3.43)  | 0.016                |
| All deaths           | 0.93 (0.79 to 1.09)  | 0.377                | 0.86 (0.70 to 1.04) | 0.118                |
|                      |                      |                      | 2.14 (1.47 to 3.11) | <0.001               |
|                      |                      |                      |                   | 1.65 (1.09 to 2.49)  | 0.018                |
| Time-dependent propensity score weights |                      |                      |                   |                      |
| Out-of-hospital deaths | 1.09 (0.88 to 1.35)  | 0.407                | 1.03 (0.80 to 1.32) | 0.822                |
|                      |                      |                      | 2.80 (1.67 to 4.71) | <0.001               |
|                      |                      |                      |                   | 2.13 (1.18 to 3.82)  | 0.013                |
| All deaths           | 1.03 (0.87 to 1.22)  | 0.113                | 0.93 (0.76 to 1.13) | 0.478                |
|                      |                      |                      | 2.03 (1.38 to 3.00) | <0.001               |
|                      |                      |                      |                   | 1.63 (1.06 to 2.51)  | 0.026                |
| Propensity score matched, covariates fixed at baseline |                      |                      |                   |                      |
| Out-of-hospital deaths | 0.95 (0.74 to 1.21)  | 0.674                | 1.04 (0.78 to 1.39) | 0.800                |
|                      |                      |                      | 2.39 (1.37 to 4.16) | 0.002               |
|                      |                      |                      |                   | 2.00 (1.01 to 3.95)  | 0.046                |

(Continued)
Discussion

In the absence of concurrent opioids, US Medicare beneficiaries 65 years of age or older without severe illness who began use of either benzodiazepine hypnotics or z-drugs had out-of-hospital and total mortality that differed little from that of comparable patients starting trazodone. In contrast, with concurrent opioids, patients receiving benzodiazepines or z-drugs had significantly increased out-of-hospital and total mortality relative to trazodone. The association with increased risk persisted with the exclusion of overdose deaths. There were no significant differences in mortality between patients receiving benzodiazepines and z-drugs, either without or with concurrent opioids.

Our finding in patients without opioid use of no significantly increased mortality for benzodiazepines or z-drugs must be interpreted cautiously. To reduce confounding by both the adverse effects of inadequate sleep [6,10] and the association of hypnotic use with life-threatening illness [45], the study comparator was a hypnotic from a different pharmacologic class. Consequently, our findings could be influenced by the cardiovascular and other adverse effects of trazodone [26,27,56]. Indeed, a 2017 clinical guideline discouraged the use of trazodone as a hypnotic [56] given the paucity of clinical trial data supporting its efficacy and safety. However, both patients and providers consider trazodone a safer alternative to benzodiazepine and z-drug hypnotics [56], and trazodone prescribing for insomnia is increasing [5]. Further studies of the efficacy and safety of trazodone for insomnia are needed.

At baseline, 12.5% of cohort members initiating treatment with benzodiazepine hypnotics had concurrent opioids, which is consistent with other reports from older populations [29–31]. Our data indicate that the hazards of concurrent use go beyond the documented association of benzodiazepines with increased opioid overdose deaths [57], which are relatively uncommon in older populations [38]. The greater than 2-fold increase in total mortality we observed, even after overdose deaths were excluded, suggests that concurrent benzodiazepine–opioid exposure poses a major risk to the health of older persons.

Although the z-drugs were introduced as a safer alternative to the benzodiazepine hypnotics [7], more recent thinking is that the adverse effects of these 2 hypnotic classes are similar [10]. However, although there is evidence of z-drug involvement in opioid overdose [58–60], unlike benzodiazepines [28], there is no “black box” FDA warning against opioid coadministration. Our findings of increased out-of-hospital and total mortality suggest that in combination with opioids, the z-drugs may be more hazardous than previously thought.

Because both hypnotics and opioids may be prescribed for patients with greater likelihood of death, a key element of our design was an active control: comparing benzodiazepines or z-drug exposure, with or without concurrent opioids, to comparable use of low-dose trazodone. Furthermore, the time-dependent propensity score analysis controlled for a large number of possible confounders. The distribution of baseline covariates in patients with concurrent opioid use indicated that patients receiving trazodone had greater comorbidity than did users of...
the other hypnotics, particularly relative to the z-drugs. Consequently, if there is residual confounding, our findings could underestimate the risks of coadministration of opioids with benzodiazepine hypnotics or z-drugs.

We postulated that the adverse cardiovascular effects of nocturnal respiratory impairment could mediate an increased risk of death for the benzodiazepines and z-drugs. However, our primary endpoint included all out-of-hospital deaths, both to avoid potentially differential under-ascertainment of cardiovascular deaths [37,46–48] and to include deaths related to other adverse respiratory effects of study hypnotics and opioids [22,36]. Although the increased risk for out-of-hospital deaths from cardiovascular causes is consistent with our hypothesis, the study data did not permit elaboration of the mechanisms of hypnotic-related deaths.

The most recent study data were for calendar 2015. Since that time, efforts to reduce opioid use have intensified, including the FDA black box warning against concurrent use with benzodiazepines [28]. Nevertheless, more recent data demonstrate continuing elevated prevalence of concurrent use of benzodiazepines and z-drugs with opioids [30,31].

The study cohort consisted of US Medicare fee-for-service beneficiaries 65 years of age or older without severe illnesses, which limits generalizability. Prescribing patterns for both hypnotics and opioids may differ in other countries. Findings may differ for younger patients (although those over 65 years of age have greater prevalence of hypnotic use [1,2,61] and increased mortality rates), those in Medicare managed care, or with substance use disorder.

There were several other study limitations. For patients receiving z-drugs with concurrent opioids, the total number of deaths was small, and the lower bound of the HR 95% CI was 1.09. Thus, a relatively small additional risk for this exposure cannot be ruled out. Although all of the study drugs are widely prescribed as hypnotics and included in guidelines for insomnia treatment [6], some benzodiazepines have other indications. However, findings did not change with exclusion of patients receiving benzodiazepines for whom the indication was most likely to be ambiguous. Study benzodiazepines only included those with a hypnotic indication or mentioned in insomnia treatment guidelines, even though other benzodiazepines are prescribed as hypnotics in clinical practice. There was no comparison to patients whose insomnia was treated with less frequently prescribed hypnotic medications or cognitive behavioral therapy. We did not examine differences between the study hypnotics for many potentially important nonfatal endpoints. Finally, the study Medicare claims data lacked more detailed patient data that could be useful for identifying patients at greatest risk of hypnotic–opioid adverse effects.

Conclusions

In US Medicare beneficiaries 65 years of age or older without concurrent opioids who initiated treatment with benzodiazepine hypnotics, z-drugs, or low-dose trazodone, study hypnotics were not associated with mortality. With concurrent opioids, benzodiazepines and z-drugs were associated with increased out-of-hospital and total mortality. These findings indicate that the dangers of benzodiazepine–opioid coadministration go beyond the documented association with overdose death and suggest that in combination with opioids, the z-drugs may be more hazardous than previously thought.

Supporting information

S1 Checklist. STROBE guideline. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology. (DOCX)
S1 Protocol. The prospective plan for study design and analysis.

(SDOCX)

S1 Appendix. Details of study methodology and additional results (Sections A–K, Tables A–H, and Fig A).

(PDF)

Author Contributions

Conceptualization: Wayne A. Ray, Cecilia P. Chung, Katherine T. Murray, Beth A. Malow, C. Michael Stein.

Data curation: James R. Daugherty.

Formal analysis: Wayne A. Ray, C. Michael Stein.

Funding acquisition: Wayne A. Ray, Cecilia P. Chung, Katherine T. Murray, Beth A. Malow, C. Michael Stein.

Investigation: Wayne A. Ray, Cecilia P. Chung, Katherine T. Murray, James R. Daugherty, C. Michael Stein.

Methodology: Wayne A. Ray, Cecilia P. Chung, Katherine T. Murray, Beth A. Malow, James R. Daugherty, C. Michael Stein.

Project administration: Wayne A. Ray.

Resources: Wayne A. Ray.

Software: James R. Daugherty.

Supervision: Wayne A. Ray, Cecilia P. Chung.

Validation: Wayne A. Ray.

Visualization: Wayne A. Ray.

Writing – original draft: Wayne A. Ray, Katherine T. Murray, C. Michael Stein.

Writing – review & editing: Wayne A. Ray, Cecilia P. Chung, Katherine T. Murray, Beth A. Malow, James R. Daugherty, C. Michael Stein.

References

1. Ford ES, Wheaton AG, Cunningham TJ, Giles WH, Chapman DP, Croft JB. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care survey 1999–2010. Sleep. 2014; 37(8):1283–93. https://doi.org/10.5665/sleep.3914 PMID: 25083008

2. Chong Y, Fryer CD, Gu Q. Prescription sleep aid use among adults: United States, 2005–2010. NCHS Data Brief. 2013; 127:1–8. PMID: 24152538

3. Kaufmann CN, Spira AP, Depp CA, Mojtabai R. Long-Term Use of Benzodiazepines and Nonbenzodiazepine Hypnotics, 1999–2014. Psychiatr Serv. 2018; 69(2):235–8. Epub 2017/11/02. https://doi.org/10.1176/appi.ps.201700095 PMID: 29089011

4. Bertisch SM, Herzig SJ, Winkelman JW, Buettner C. National use of prescription medications for insomnia: NHANES 1999–2010. Sleep. 2014; 37(2):343–9. https://doi.org/10.5665/sleep.3410 PMID: 24497662

5. Wong J, Murray Horwitz M, Bertisch SM, Herzig SJ, Buysse DJ, Toh S. Trends in Dispensing of Zolpidem and Low-Dose Trazodone Among Commercially Insured Adults in the United States, 2011–2018. JAMA. 2020; 324(21):2211–3. Epub 2020/12/02. https://doi.org/10.1001/jama.2020.19224 PMID: 33258882
6. Buysse DJ. Insomnia. JAMA. 2013; 309(7):706–16. https://doi.org/10.1001/jama.2013.193 PMID: 23423416

7. Sanger DJ, Benavides J, Perrault G, Morel E, Cohen C, Joly D, et al. Recent developments in the behavioral pharmacology of benzodiazepine (omega) receptors: evidence for the functional significance of receptor subtypes. Neurosci Biobehav Rev. 1994; 18(3):355–72. https://doi.org/10.1016/0149-7634(94)90049-3 PMID: 7894354

8. Drugs for insomnia. Med Lett Drugs Ther. 2015; 57(1472):95–8. PMID: 26147892

9. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016. https://doi.org/10.7326/M15-2175 PMID: 27136449

10. Winkelman JW. Clinical practice: Insomnia disorder. N Engl J Med. 2015; 373(15):1437–44. https://doi.org/10.1056/NEJMcp1412740 PMID: 26444730

11. Bossini L, Casolaro I, Koukouna D, Cecchini F, Fagioli A. Off-label uses of trazodone: a review. Expert Opin Pharmacother. 2012; 13(12):1707–17. https://doi.org/10.1517/14656662.2012.699523 PMID: 22712761

12. Fagioli A, Comandini A, Catena Dell'Osso M, Kasper S. Rediscovering trazodone for the treatment of major depressive disorder. CNS Drugs. 2012; 26(12):1033–49. https://doi.org/10.1007/s40263-012-0010-5 PMID: 23192413

13. Generali JA, Cada DJ. Trazodone: Insomnia (Adults). Hosp Pharm. 2015; 50(5):367–9. https://doi.org/10.1310/hpj0505-367 PMID: 26143690

14. Guilleminault C. Insomnia in Elderly Patients: Recommendations for Pharmacological Management. Drugs Aging. 2018; 35(9):791–817. Epub 2018/07/31. https://doi.org/10.1007/s40266-018-0569-8 PMID: 30058034

15. Clergue F, Desmonts JM, Duvaldestin P, Salaun G. Depression of respiratory drive by diazepam as premedication. Br J Anaesth. 1981; 53(10):1059–63. Epub 1981/10/01. https://doi.org/10.1093/bja/53.10.1059 PMID: 6794583

16. Abad VC, Guillen-Artigues R, Forcada MP, Tobes V, Alavedra J. The acute effects of zolpidem compared to diazepam using radio-telemetry. Neuropharmacology. 2001; 40(5):717–21. https://doi.org/10.1016/s0028-3908(00)00196-9 PMID: 11311900

17. Elliot EE, White JM. The acute effects of zolpidem compared to diazepam and lorazepam using radio-telemetry. Neuropharmacology. 2001; 40(5):717–21. https://doi.org/10.1016/s0028-3908(00)00196-9 PMID: 11311900

18. Eckert DJ, Malhotra A, Wellman A, White DP. Trazodone increases the respiratory arousal threshold in patients with obstructive sleep apnea and a low arousal threshold. Sleep. 2014; 37(4):811–9. https://doi.org/10.5665/sleep.3596 PMID: 24899767

19. Smales ET, Edwards BA, Deyoung PN, McSharry DG, Wellman A, Velasquez A, et al. Trazodone effects on obstructive sleep apnea and non-REM arousal threshold. Ann Am Thorac Soc. 2015; 12(5):758–64. https://doi.org/10.1513/AnnalsATS.201408-399OC PMID: 25719754

20. Service JA, Waring WS. QT prolongation and delayed atrioventricular conduction caused by acute ingestion of trazodone. Clin Toxicol. 2008; 46:71–3. https://doi.org/10.1080/15563650701275322 PMID: 18167038
27. Jaffer KY, Chang T, Vanle B, Dang J, Steiner AJ, Loera N, et al. Trazodone for Insomnia: A Systematic Review. Innov Clin Neurosci. 2017; 14(7–8):24–34. Epub 2018/03/20. PMID: 29552421

28. Aschenbrenner DS. FDA Strengthens Warning Concerning Coadministration of Opioids and Benzodiazepines. Am J Nurs. 2016; 116(12):24–5. Epub 2016/11/23. https://doi.org/10.1097/01.NAJ.0000508667.18716.ae PMID: 27875443

29. Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002–2014. Am J Prev Med. 2016. https://doi.org/10.1016/j.amepre.2016.02.014 PMID: 27079639

30. Jeffery MM, Hooten WM, Jena AB, Ross JS, Shah ND, Karaca-Mandic P. Rates of Physician Co-prescribing of Opioids and Benzodiazepines After the Release of the Centers for Disease Control and Prevention Guidelines in 2016. JAMA Netw Open. 2019; 2(8):e198325. Epub 2019/08/03. https://doi.org/10.1001/jamanetworkopen.2019.8325 PMID: 31373650

31. Tori ME, Larochelle MR, Naimi TS. Alcohol or Benzodiazepine Co-involvement With Opioid Overdose Deaths in the United States, 1999–2017. JAMA Netw Open. 2020; 3(4):e202361. Epub 2020/04/10. https://doi.org/10.1001/jamanetworkopen.2020.2361 PMID: 32271389

32. Zutler M, Holty JE. Opioids, sleep, and sleep-disordered breathing. Curr Pharm Des. 2011; 17(15):1443–9. https://doi.org/10.2174/138161211796197070 PMID: 21476955

33. Boyer EW. Management of opioid analgesic overdose. N Engl J Med. 2012; 367:146–55. https://doi.org/10.1056/NEJMc1104348 PMID: 22458868

34. Yue HJ, Guilleminault C. Opioid medication and sleep-disordered breathing. Med Clin North Am. 2010; 94(3):435–46. https://doi.org/10.1016/j.mcna.2010.02.007 PMID: 20451025

35. Webster LR, Choi Y, Desai H, Webster L, Grant BJ. Sleep-disordered breathing and chronic opioid therapy. Pain Med. 2008; 9(4):425–32. https://doi.org/10.1111/j.1526-4637.2007.00343.x PMID: 18489633

36. Macintyre PE, Loadsman JA, Scott DA. Opioids, ventilation and acute pain management. Anaesth Intensive Care. 2011; 39(3):435–46. https://doi.org/10.1016/j.mcna.2010.02.007 PMID: 20451025

37. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. Clin J Pain. 2008; 24:521–7. https://doi.org/10.1097/AJP.0b013e318169d8d3 PMID: 18574361

38. Ray WA. Evaluating medication effects outside of clinical trials: New-user designs. Am J Epidemiol. 2003; 158:915–20. https://doi.org/10.1093/aje/kwg231 PMID: 14573730

39. Graham DJ, Reichman ME, Wernecke M, Hsueh YH, Izem R, Southworth MR, et al. Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Non-valvular Atrial Fibrillation. JAMA Intern Med. 2016; 176(11):1662–71. Epub 2016/10/04. https://doi.org/10.1001/jamainternmed.2016.5954 PMID: 27695821

40. CMS. Medicare Part D Enrollment: Part D Enrollees by Type of Plan, Low Income Subsidy (LIS), and Retiree Drug Subsidy, by Demographic Characteristics, Calendar Year 2019 n.d. [cited 2021 May 5]. Available from: https://www.cms.gov/files/document/2019cpsmdrende2.pdf.

41. CMS. Chronic Conditions Data Warehouse. [cited 2021 May 13]. Available from: https://www2.ccwdata.org/web/guest/home/.

42. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Hypnotic-opioid mortality

43. Von Korff M, Saunders K, Ray GT, Boudreau D, Campbell C, Merrill J, et al. De facto long-term opioid therapy for noncancer pain. Clin J Pain. 2008; 24:521–7. https://doi.org/10.1097/AJP.0b013e318169d8d3 PMID: 18574361

44. Ray WA. Evaluating medication effects outside of clinical trials: New-user designs. Am J Epidemiol. 2003; 158:915–20. https://doi.org/10.1093/aje/kwg231 PMID: 14573730

45. Neutel CI, Johansen HL. Hypnotic-opioid mortality

46. Ray WA, Chung CP, Murray KT, Cooper W, Hall K, Stein CM. Out-of-hospital mortality among patients receiving methadone for noncancer pain. JAMA Intern Med. 2015; 175(3):420–7. https://doi.org/10.1001/jamainternmed.2014.6294 PMID: 25999329

47. Johnson CJ, Hahn CG, Fink AK, German RR. Variability in cancer death certificate accuracy by characteristics of death certifiers. Am J Forensic Med Pathol. 2012; 33(2):137–42. Epub 2011/04/15. https://doi.org/10.1097/PAF.0b013e318219877e PMID: 21490500

48. Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. Pharmacoepidemiol Drug Saf. 2010; 19(6):563–72. https://doi.org/10.1002/pds.1888 PMID: 20029623
49. Simard M, Sirois C, Candas B. Validation of the Combined Comorbidity Index of Charlson and Elixhauser to Predict 30-Day Mortality Across ICD-9 and ICD-10. Med Care. 2018; 56(5):441–7. Epub 2018/03/27. https://doi.org/10.1097/MLR.0000000000000905 PMID: 29578951

50. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005; 43(11):1130–9. Epub 2005/10/15. https://doi.org/10.1097/01.mlr.0000182534.19832.83 PMID: 16224307

51. Kim DH, Schneeweiss S, Glynn RJ, Lipsitz LA, Rockwood K, Avorn J. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. J Gerontol A Biol Sci Med Sci. 2018; 73(7):980–7. Epub 2017/12/16. https://doi.org/10.1093/gerona/glx229 PMID: 29244057

52. Austin PC. An introduction to propensity score methods for reducing the effects of confounding on observational studies. Multivar Behav Res. 2011; 46:399–424. https://doi.org/10.1080/00273171.2011.568786 PMID: 21818162

53. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med. 2013; 32(19):3388–414. Epub 2013/03/20. https://doi.org/10.1002/sim.5753 PMID: 23508673

54. Ray WA, Liu Q, Shepherd BE. Performance of time-dependent propensity scores: a pharmacoepidemiology case study. Pharmacoepidemiol Drug Saf. 2015; 32:98–106. https://doi.org/10.1002/pds.3727 PMID: 25408360

55. Allison PD. Survival Analysis Using SAS. A Practical Guide. 2nd ed. Cary, NC: SAS Institute; 2010.

56. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017; 13(2):307–49. Epub 2016/12/22. https://doi.org/10.5664/jcsm.6470 PMID: 27998379

57. Park TW, Saltz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ. 2015; 350:h2698. https://doi.org/10.1136/bmj.h2698 PMID: 26063215

58. Turner BJ, Liang Y. Drug overdose in a retrospective cohort with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: Interactions with mental health disorders. J Gen Intern Med. 2015; 30(8):1081–96. https://doi.org/10.1007/s11606-015-3199-4 PMID: 25850263

59. Macleod J, Steer C, Tilling K, Cornish R, Marsden J, Miller T, et al. Prescription of benzodiazepines, z-drugs, and gabapentinoids and mortality risk in people receiving opioid agonist treatment: Observational study based on the UK Clinical Practice Research Datalink and Office for National Statistics death records. PLoS Med. 2019; 16(11):e1002965. Epub 2019/11/27. https://doi.org/10.1371/journal.pmed.1002965 PMID: 31770388

60. Abrahamsson T, Berge J, Öjehagen A, Häkansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment: A nation-wide register-based open cohort study. Drug Alcohol Depend. 2017; 174:58–64. Epub 2017/03/21. https://doi.org/10.1016/j.drugalcdep.2017.01.013 PMID: 28315808

61. Olsson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiatry. 2015; 72(2):136–42. Epub 2014/12/18. https://doi.org/10.1001/jamapsychiatry.2014.1763 PMID: 25517224