

Appendix: Supplemental Content [posted as supplied by author]

Table A. List of Opioids and Benzodiazepines

Opioids
fentanyl (patch or oral form), hydrocodone, hydromorphone (oral form), methadone, morphine, oxymorphone, oxycodone
Benzodiazepines
alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, oxazepam, prazepam, quazepam, temazepam, triazolam.

Table B. List of Medical Comorbidities and ICD-9 Codes

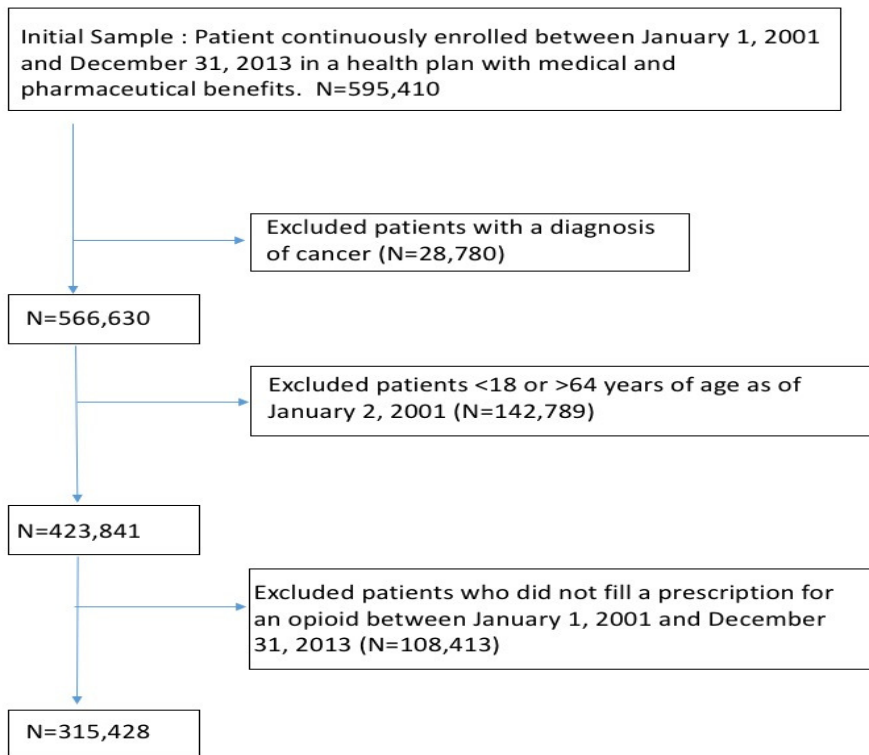
Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
Peripheral Vascular Disease	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4
Hypertension	401-405
Chronic Obstructive Pulmonary Disease	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8
Diabetes Mellitus	250.x
Chronic Kidney Disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Cancer	140.x-172.x, 174.x-202.x, 203.0, 238.6
Cerebrovascular Disease	430.x-438.x
Myocardial Infarction	410.x, 412.x
Dementia	290.x
Liver Disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0-456.2, 570.x, 571.x, 572.2-572.8, 573.3, 573.4, 573.8, 573.9, V42.7
Alcohol Abuse	265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3
Drug Abuse	292.x, 304.x, 305.2-305.9, V65.42
Psychosis	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x
Depression	296.2, 296.3, 296.5, 300.4, 309.x, 311

Table C Results of Sensitivity Analyses Examining Alternative Model Definitions

Concurrent Use Definition	Opioid Overdose Event Definition	OR, All Users	OR, Intermittent Users	OR, Chronic Users
At least one day overlap	Within 7 days last opioid prescription	2.14 (2.05, 2.24) p<0.001	1.42 (1.33, 1.51) p<0.001	1.81 (1.67, 1.96) p<0.001
At least one day overlap	Within 30 days last opioid prescription	2.09 (2.00, 2.17) p<0.001	1.49 (1.41, 1.58) p<0.001	1.75 (1.62, 1.89) p<0.001
>25% overlap	Within 7 days last opioid prescription	1.88 (1.78, 1.97) p<0.001	1.26 (1.18, 1.35) p<0.001	1.62 (1.49, 1.76) p<0.001
>25% overlap	Within 30 days last opioid prescription	1.82 (1.73, 1.90) p<0.001	1.32 (1.24, 1.40) p<0.001	1.55 (1.43, 1.67) p<0.001

Table C reports the results of sensitivity analyses in which we considered alternate definitions of concurrent benzodiazepine/opioid use as well as alternative definitions of an opioid overdose event. Our baseline analysis (shown in the first row) defined concomitant benzodiazepine/opioid use as having at least one day of overlap between the time period covered by a benzodiazepine prescription and an opioid prescription, and defined an opioid overdose event as an emergency room visit or inpatient admission for opioid overdose occurring during the time period covered by an opioid prescription or within 7 days following the end of this time period. We considered an alternative definition for concurrent use that required at least 25% of the annual days of opioid supply to overlap with a benzodiazepine prescription. In addition, we considered an alternate definition for opioid overdose that allowed for as an emergency room visit or inpatient admission for opioid overdose that occurred within 30 days following the end of the time period covered by an opioid prescription. The table shows the odds ratio for an opioid overdose event after adjusting for age, gender, year, and the medical comorbidities listed in table 1. 95% confidence intervals are shown in parentheses and were calculated using standard errors that were adjusted for clustering at the patient level.

Fig A. Sample Construction Flow Diagram



Technical Appendix.

This technical appendix briefly outlines how we obtained age-adjusted measures of opioid utilization and benzodiazepine co-prescribing. We obtained age-adjusted measures of these values because our sample consists of persons who were continuously enrolled between 2001 and 2013. As a result, the age of each person in our sample (and therefore the age distribution of the sample itself) increases by one year each year.

We obtained age-adjusted estimates by estimating the following logistic regression:

$$outcome_{it} = \delta_t + \Gamma_i + \varepsilon_{it} \quad (1)$$

In the equation above, i indexes individuals, and t indexes the year. $outcome_{it}$, the dependent variable, is a indicator variable that equals one if patient i experienced the given outcome in year t and zero otherwise. For example, in the case of benzodiazepine co-prescribing, $outcome_{it}$ would equal one if the patient was co-prescribed a benzodiazepine in year t and zero otherwise. δ_t is a vector of year effects, i.e., it is a vector of indicator variables equaling one for the given year and zero otherwise (e.g., one variable equaling one if the given year is 2001 and zero otherwise, another variable equaling one if the given year is 2002 and zero otherwise, etc). Similarly, Γ_i is a vector of age effects (one age effect for each 5 year age group starting at age 18). ε_{it} is the error term.

After estimating the logistic regression outlined in equation (1), we then obtained the age-adjusted estimate for the given year by using our regression model to calculate the predicted value for the outcome, setting the indicator variable for the given year equal to one (and all other year variables equal to zero), and setting age indicators equal to their average values for the entire sample. For example, to obtain age-adjusted estimates for 2001, we obtained the predicted values from the regression by setting the year effect for 2001 to equal one and setting the remaining year effects equal to zero. As noted above, we set the age effects equal to their mean values for the entire sample.