

## Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

**eTable 1. Drug Exposure Definitions**

| <b>Drug class</b>    | <b>Generic names</b>                                                                                                                                                                                                                                 |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Opioid</i>        | alfentanil, buprenorphine, butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphan, meperidine, methadone, morphine, oxycodone, oxymorphone, propoxyphene, pentazocine, remifentanil, sufentanil, tapentadol, tramadol |
| <i>Gabapentinoid</i> | gabapentin, pregabalin                                                                                                                                                                                                                               |

**eTable 2. Outcome Definitions**

| Outcome                   | ICD-9 Definition                                                                                                                                                                                                                                                                                                                           | ICD-10 definition (last digit * stands for any, which will be A or D or S)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Opioid overdose           | <p>965.00 Poisoning by opium (alkaloids) unspecified</p> <p>965.02 Poisoning by methadone</p> <p>965.09 Poisoning by other opiates and related narcotics</p> <p>E850.1 Accidental poisoning by methadone</p> <p>E850.2 Accidental poisoning by other opiates and related narcotics</p> <p><b>AND</b></p> <p>Charge code for naloxone</p>   | <p>T400X1* Poisoning by opium, accidental</p> <p>T400X2* intentional self-harm</p> <p>T400X3* assault</p> <p>T400X4* undetermined</p> <p>T402X1* Poisoning by other opioids, accidental</p> <p>T402X2* intentional self-harm</p> <p>T402X3* assault</p> <p>T402X4* undetermined</p> <p>T403X1* Poisoning by methadone, accidental</p> <p>T403X2* intentional self-harm</p> <p>T403X3* assault</p> <p>T403X4* undetermined</p> <p>T404X1* Poisoning by other synthetic narcotics, accidental</p> <p>T404X2* intentional self-harm</p> <p>T404X3* assault</p> <p>T404X4* undetermined</p> <p>T40601* Poisoning by unspecified narcotics, accidental</p> <p>T40602* intentional self-harm</p> <p>T40603* assault</p> <p>T40604* undetermined</p> <p>T40691* Poisoning by other narcotics, accidental</p> <p>T40692* intentional self-harm</p> <p>T40693* assault</p> <p>T40694* undetermined</p> <p><b>AND</b></p> <p>Charge code for naloxone</p> |
| Respiratory complications | <p>51881 Acute respiratory failure</p> <p>51882 Other pulmonary insufficiency, not elsewhere classified</p> <p>78603 Apnea</p> <p>78605 Shortness of breath</p> <p>78609 Other respiratory abnormalities</p> <p>79901 Asphyxia</p> <p>79902 Hypoxemia</p> <p>7991 Respiratory arrest</p> <p><b>AND</b></p> <p>Charge code for naloxone</p> | <p>J9600 Acute respiratory failure, unspecified whether with hypoxia or hypercapnia</p> <p>J9601 Acute respiratory failure with hypoxia</p> <p>J9602 Acute respiratory failure with hypercapnia</p> <p>J9690 Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia</p> <p>J9691 Respiratory failure, unspecified with hypoxia</p> <p>J9692 Respiratory failure, unspecified with hypercapnia</p> <p>J80 Acute respiratory distress syndrome</p> <p>R0603 Acute respiratory distress</p> <p>R0681 Apnea, not elsewhere classified</p> <p>R0602 Shortness of breath</p> <p>R0600 Dyspnea, unspecified</p> <p>R0609 Other forms of dyspnea</p> <p>R0689 Other abnormalities of breathing</p> <p>R0901 Asphyxia</p> <p>R0902 Hypoxemia</p> <p>R092 Respiratory arrest</p> <p><b>AND</b></p> <p>Charge code for naloxone</p>                                                                                             |
| Unspecified adverse       | E9351 Methadone causing adverse effects in therapeutic use                                                                                                                                                                                                                                                                                 | <p>T403X5* Adverse effect of methadone</p> <p>T400X5* Adverse effect of opium</p> <p>T402X5* Adverse effect of other opioids</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|                       |                                                                                                                                         |                                                                                                                                                                                               |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| effects of<br>opioids | E9352 Other opiates and<br>related narcotics causing<br>adverse effects in therapeutic<br>use<br><b>AND</b><br>Charge code for naloxone | T404X5* Adverse effect of other synthetic narcotics<br>T40605* Adverse effect of unspecified narcotics<br>T40695* Adverse effect of other narcotics<br><b>AND</b><br>Charge code for naloxone |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**eTable 3. Baseline Patient Characteristics With Standardized Differences**

|                                                       | Unadjusted     |                          |                | Propensity score adjusted |                          |                |
|-------------------------------------------------------|----------------|--------------------------|----------------|---------------------------|--------------------------|----------------|
|                                                       | Opioids only   | Gabapentinoids + opioids | Std. diff. (%) | Opioids only              | Gabapentinoids + opioids | Std. diff. (%) |
|                                                       | N = 4,655,183  | N = 892,484              |                | N = 3,002,480             | N = 737,383              |                |
| <b>Demographic characteristics</b>                    |                |                          |                |                           |                          |                |
| Age, mean (SD), y                                     | 63.7 (14.7)    | 63.5 (11.8)              | -1.8           | 63.6 (12.0)               | 63.6 (12.0)              | -0.2           |
| Male sex - no. (%)                                    | 1913284 (41.1) | 353315 (39.6)            | -3.1           | 1241483 (41.3)            | 302076 (41.0)            | -0.8           |
| Race - no. (%)                                        |                |                          |                |                           |                          |                |
| White                                                 | 3623681 (77.8) | 731816 (82.0)            | 10.4           | 2456587 (81.8)            | 602586 (81.7)            | -0.3           |
| Black                                                 | 403615 (8.7)   | 73439 (8.2)              | -1.6           | 241575 (8)                | 60131 (8.2)              | 0.4            |
| Other                                                 | 627887 (13.5)  | 87229 (9.8)              | -11.6          | 304318 (10.1)             | 74666 (10.1)             | 0.0            |
| <b>Surgical characteristics</b>                       |                |                          |                |                           |                          |                |
| Type of admission - no. (%)                           |                |                          |                |                           |                          |                |
| Non-emergency                                         | 3520865 (75.6) | 672130 (75.3)            | -0.8           | 2321564 (77.3)            | 567558 (77.0)            | -0.8           |
| Emergency                                             | 193241 (4.2)   | 3801 (0.4)               | -25.1          | 6608 (0.2)                | 2113 (0.3)               | 1.3            |
| Clinic                                                | 648664 (13.9)  | 198232 (22.2)            | 21.6           | 614556 (20.5)             | 153530 (20.8)            | 0.9            |
| Other                                                 | 292413 (6.3)   | 18321 (2.1)              | -21.3          | 59753 (2.0)               | 14182 (1.9)              | -0.5           |
| Pre-procedure LOS, mean (SD), days                    | 0.7 (2.2)      | 0.1 (0.7)                | -37.2          | 0 (0.3)                   | 0 (0.2)                  | -4.3           |
| <b>Procedure - no. (%)</b>                            |                |                          |                |                           |                          |                |
| Cholecystectomy                                       | 88590 (1.9)    | 2096 (0.2)               | -16.3          | 3962 (0.1)                | 1326 (0.2)               | 1.2            |
| Colorectal resection                                  | 365300 (7.8)   | 17616 (2.0)              | -27.4          | 52120 (1.7)               | 15768 (2.1)              | 2.9            |
| Coronary artery bypass graft                          | 430558 (9.2)   | 7458 (0.8)               | -39.2          | 11972 (0.4)               | 2461 (0.3)               | -1.1           |
| Cystectomy                                            | 14455 (0.3)    | 521 (0.1)                | -5.9           | 1156 (0)                  | 388 (0.1)                | 0.7            |
| Esophagectomy                                         | 7864 (0.2)     | 133 (0.0)                | -5.1           | 72 (0.0)                  | 52 (0.0)                 | 0.7            |
| Gastrectomy                                           | 35880 (0.8)    | 666 (0.1)                | -10.7          | 693 (0.0)                 | 327 (0.0)                | 1.2            |
| Hip arthroplasty                                      | 706096 (15.2)  | 213259 (23.9)            | 22.1           | 715168 (23.8)             | 176347 (23.9)            | 0.2            |
| Hysterectomy                                          | 391276 (8.4)   | 13616 (1.5)              | -32.1          | 27691 (0.9)               | 9851 (1.3)               | 3.9            |
| Knee arthroplasty                                     | 1014527 (21.8) | 394692 (44.2)            | 49.1           | 1300498 (43.3)            | 316426 (42.9)            | -0.8           |
| Laminectomy or spinal fusion                          | 888097 (19.1)  | 208234 (23.3)            | 10.4           | 787903 (26.2)             | 188429 (25.6)            | -1.6           |
| Lobectomy                                             | 58581 (1.3)    | 3849 (0.4)               | -9.0           | 13294 (0.4)               | 3345 (0.5)               | 0.2            |
| Mastectomy                                            | 107153 (2.3)   | 5840 (0.7)               | -13.7          | 17633 (0.6)               | 4736 (0.6)               | 0.7            |
| Nephrectomy                                           | 89062 (1.9)    | 3870 (0.4)               | -13.8          | 10017 (0.3)               | 2871 (0.4)               | 0.9            |
| Pancreatectomy                                        | 14888 (0.3)    | 612 (0.1)                | -5.7           | 1600 (0.1)                | 516 (0.1)                | 0.7            |
| Surgery for hip fracture or dislocation               | 442856 (9.5)   | 20022 (2.2)              | -31.3          | 58702 (2.0)               | 14540 (2.0)              | 0.1            |
| <b>Type of opioid on the day of surgery - no. (%)</b> |                |                          |                |                           |                          |                |

|                                                       |                |               |       |                |               |      |
|-------------------------------------------------------|----------------|---------------|-------|----------------|---------------|------|
| Oxycodone                                             | 1256948 (27.0) | 491374 (55.1) | 59.5  | 1520293 (50.6) | 373251 (50.6) | 0.0  |
| Morphine                                              | 2546617 (54.7) | 411980 (46.2) | -17.2 | 1465881 (48.8) | 356482 (48.3) | -1.0 |
| Meperidine                                            | 436666 (9.4)   | 58281 (6.5)   | -10.5 | 213250 (7.1)   | 51655 (7.0)   | -0.4 |
| Hydromorphone                                         | 2554461 (54.9) | 532919 (59.7) | 9.8   | 1828710 (60.9) | 446088 (60.5) | -0.8 |
| Hydrocodone                                           | 660566 (14.2)  | 142143 (15.9) | 4.9   | 505744 (16.8)  | 121919 (16.5) | -0.8 |
| Fentanyl                                              | 3742110 (80.4) | 717097 (80.3) | -0.1  | 2426260 (80.8) | 594835 (80.7) | -0.4 |
| Tramadol                                              | 168638 (3.6)   | 94116 (10.5)  | 27.2  | 201755 (6.7)   | 51528 (7.0)   | 1.1  |
| Other                                                 | 376316 (8.1)   | 66553 (7.5)   | -2.3  | 230111 (7.7)   | 55303 (7.5)   | -0.6 |
| Total MMEs on the day of surgery, mean (SD)           | 307.3 (366.3)  | 277.1 (350.7) | -8.4  | 283.8 (356.7)  | 283.2 (357.2) | -0.2 |
| Intravenous opioids                                   | 4520470 (97.1) | 851604 (95.4) | -8.9  | 2886162 (96.1) | 708116 (96.0) | -0.5 |
| <b>Medication use on the day of surgery - no. (%)</b> |                |               |       |                |               |      |
| Anticonvulsant agents                                 | 84534 (1.8)    | 27705 (3.1)   | 8.3   | 69761 (2.3)    | 17739 (2.4)   | 0.5  |
| Antidepressants                                       | 495662 (10.6)  | 175064 (19.6) | 25.2  | 461115 (15.4)  | 115327 (15.6) | 0.8  |
| Antipsychotic agents                                  | 109188 (2.3)   | 25926 (2.9)   | 3.5   | 69813 (2.3)    | 17284 (2.3)   | 0.1  |
| Barbiturates                                          | 1674 (0.0)     | 187 (0.0)     | -0.9  | 690 (0.0)      | 157 (0.0)     | -0.1 |
| Benzodiazepines                                       | 3601887 (77.4) | 742998 (83.3) | 14.8  | 2499824 (83.3) | 611754 (83)   | -0.8 |
| Dementia medications                                  | 66635 (1.4)    | 7713 (0.9)    | -5.3  | 23086 (0.8)    | 5602 (0.8)    | -0.1 |
| Hypnotic agents                                       | 311169 (6.7)   | 53838 (6.0)   | -2.7  | 170011 (5.7)   | 41710 (5.7)   | 0.0  |
| Lithium                                               | 6360 (0.1)     | 1994 (0.2)    | 2.0   | 5735 (0.2)     | 1393 (0.2)    | 0.0  |
| Muscle relaxants                                      | 403282 (8.7)   | 149068 (16.7) | 24.3  | 453277 (15.1)  | 112412 (15.2) | 0.4  |
| NSAIDs                                                | 1349137 (29)   | 365260 (40.9) | 25.2  | 1178390 (39.2) | 290888 (39.4) | 0.4  |
| <b>Comorbidities - no. (%)</b>                        |                |               |       |                |               |      |
| Alcohol abuse or dependence                           | 102626 (2.2)   | 12984 (1.5)   | -5.6  | 43035 (1.4)    | 10522 (1.4)   | -0.1 |
| Anxiety                                               | 440787 (9.5)   | 119444 (13.4) | 12.3  | 344814 (11.5)  | 85398 (11.6)  | 0.3  |
| Bipolar disorder                                      | 51543 (1.1)    | 15033 (1.7)   | 4.9   | 39082 (1.3)    | 9867 (1.3)    | 0.3  |
| Cancer                                                | 512219 (11.0)  | 32183 (3.6)   | -28.7 | 98626 (3.3)    | 26530 (3.6)   | 1.7  |
| Chronic renal insufficiency                           | 364751 (7.8)   | 54252 (6.1)   | -6.9  | 163872 (5.5)   | 40323 (5.5)   | 0.0  |
| Congestive heart failure                              | 316395 (6.8)   | 30430 (3.4)   | -15.4 | 89835 (3.0)    | 22156 (3.0)   | 0.1  |
| COPD or asthma                                        | 774092 (16.6)  | 159483 (17.9) | 3.3   | 490891 (16.3)  | 120767 (16.4) | 0.1  |
| Dementia                                              | 220705 (4.7)   | 12440 (1.4)   | -19.5 | 37997 (1.3)    | 9565 (1.3)    | 0.3  |
| Depression                                            | 565720 (12.2)  | 152551 (17.1) | 14.0  | 451486 (15)    | 111117 (15.1) | 0.1  |
| Diabetes                                              | 990112 (21.3)  | 206169 (23.1) | 4.4   | 627837 (20.9)  | 154147 (20.9) | 0.0  |
| Liver disease                                         | 140867 (3.0)   | 19612 (2.2)   | -5.2  | 58621 (2.0)    | 14681 (2.0)   | 0.3  |
| Psychosis                                             | 40670 (0.9)    | 5007 (0.6)    | -3.7  | 15232 (0.5)    | 3814 (0.5)    | 0.1  |
| Back and neck pain without neuropathic involvement    | 874168 (18.8)  | 217794 (24.4) | 13.7  | 766703 (25.5)  | 184436 (25)   | -1.2 |
| Diabetic neuropathy                                   | 61807 (1.3)    | 26202 (2.9)   | 11.2  | 41781 (1.4)    | 11253 (1.5)   | 1.1  |
| Fibromyalgia                                          | 72141 (1.5)    | 38151 (4.3)   | 16.3  | 73783 (2.5)    | 19930 (2.7)   | 1.5  |

|                                                             |                |               |       |                |               |      |
|-------------------------------------------------------------|----------------|---------------|-------|----------------|---------------|------|
| Postherpetic neuralgia                                      | 1606 (0.0)     | 884 (0.1)     | 2.5   | 1312 (0.0)     | 375 (0.1)     | 0.3  |
| Other neuropathic pain                                      | 275317 (5.9)   | 93669 (10.5)  | 16.8  | 289897 (9.7)   | 69491 (9.4)   | -0.8 |
| Osteoarthritis                                              | 1718672 (36.9) | 597969 (67)   | 63.1  | 1976068 (65.8) | 482807 (65.5) | -0.7 |
| Rheumatoid arthritis                                        | 111347 (2.4)   | 32887 (3.7)   | 7.5   | 98064 (3.3)    | 24010 (3.3)   | -0.1 |
| Other arthritis, arthropathies and musculoskeletal pain     | 593161 (12.7)  | 131643 (14.8) | 5.8   | 450616 (15.0)  | 109151 (14.8) | -0.6 |
| Combined comorbidity score, mean (SD)                       | 1.0 (2.2)      | 0.4 (1.5)     | -30.9 | 0.3 (1.5)      | 0.3 (1.5)     | 1.2  |
| <b>Inpatient use of medication before surgery - no. (%)</b> |                |               |       |                |               |      |
| Anticonvulsant agents                                       | 24474 (0.5)    | 449 (0.1)     | -8.9  | 942 (0.0)      | 180 (0.0)     | -0.4 |
| Antidepressants                                             | 159342 (3.4)   | 3055 (0.3)    | -22.8 | 6916 (0.2)     | 1238 (0.2)    | -1.4 |
| Antipsychotic agents                                        | 47864 (1.0)    | 653 (0.1)     | -12.9 | 1123 (0.0)     | 226 (0.0)     | -0.4 |
| Barbiturates                                                | 726 (0.0)      | 5 (0.0)       | -1.7  | 4 (0.0)        | 1 (0.0)       | 0.0  |
| Benzodiazepines                                             | 492798 (10.6)  | 9801 (1.1)    | -41.3 | 24057 (0.8)    | 4710 (0.6)    | -1.9 |
| Dementia medications                                        | 39145 (0.8)    | 400 (0.0)     | -12.0 | 383 (0.0)      | 65 (0.0)      | -0.4 |
| Hypnotic agents                                             | 84860 (1.8)    | 1499 (0.2)    | -16.7 | 3540 (0.1)     | 598 (0.1)     | -1.2 |
| Lithium                                                     | 1297 (0.0)     | 28 (0.0)      | -2.0  | 70 (0.0)       | 16 (0.0)      | 0.0  |
| Muscle relaxants                                            | 55763 (1.2)    | 2179 (0.2)    | -11.3 | 6909 (0.2)     | 1309 (0.2)    | -1.2 |
| NSAIDs                                                      | 102626 (2.2)   | 5615 (0.6)    | -13.4 | 17280 (0.6)    | 4159 (0.6)    | -0.2 |
| Opioids                                                     | 986666 (21.2)  | 31111 (3.5)   | -55.9 | 85452 (2.8)    | 20052 (2.7)   | -0.8 |
| <b>Hospital characteristics - no. (%)</b>                   |                |               |       |                |               |      |
| Region                                                      |                |               |       |                |               |      |
| Northeast                                                   | 702680 (15.1)  | 139481 (15.6) | 1.5   | 483416 (16.1)  | 115323 (15.6) | -1.3 |
| South                                                       | 2165560 (46.5) | 390788 (43.8) | -5.5  | 1325232 (44.1) | 326867 (44.3) | 0.4  |
| Midwest                                                     | 905863 (19.5)  | 181127 (20.3) | 2.1   | 601615 (20.0)  | 148633 (20.2) | 0.3  |
| West                                                        | 881080 (18.9)  | 181088 (20.3) | 3.4   | 592217 (19.7)  | 146560 (19.9) | 0.4  |
| Number of beds                                              |                |               |       |                |               |      |
| 000-099                                                     | 168049 (3.6)   | 42231 (4.7)   | 5.6   | 135052 (4.5)   | 33490 (4.5)   | 0.2  |
| 100-199                                                     | 548080 (11.8)  | 124547 (14)   | 6.5   | 435261 (14.5)  | 106699 (14.5) | -0.1 |
| 200-299                                                     | 780745 (16.8)  | 153254 (17.2) | 1.1   | 520496 (17.3)  | 128213 (17.4) | 0.1  |
| 300-399                                                     | 876128 (18.8)  | 151675 (17.0) | -4.8  | 529583 (17.6)  | 129732 (17.6) | -0.1 |
| 400-499                                                     | 748654 (16.1)  | 135213 (15.2) | -2.6  | 449842 (15.0)  | 108639 (14.7) | -0.7 |
| 500+                                                        | 1533527 (32.9) | 285564 (32.0) | -2.0  | 932246 (31.0)  | 230610 (31.3) | 0.5  |
| Teaching Hospital                                           | 2004246 (43.1) | 406377 (45.5) | 5.0   | 1328736 (44.3) | 325491 (44.1) | -0.2 |
| Rural Hospital                                              | 462378 (9.9)   | 84877 (9.5)   | -1.4  | 287198 (9.6)   | 69390 (9.4)   | -0.5 |
| <b>Admission Year_Quarter - no. (%)</b>                     |                |               |       |                |               |      |
| 2007_4                                                      | 89688 (1.9)    | 5085 (0.6)    | -12.2 | 18050 (0.6)    | 4522 (0.6)    | 0.2  |
| 2008_1                                                      | 90192 (1.9)    | 5870 (0.7)    | -11.3 | 21205 (0.7)    | 5364 (0.7)    | 0.3  |
| 2008_2                                                      | 89910 (1.9)    | 6315 (0.7)    | -10.7 | 23029 (0.8)    | 5744 (0.8)    | 0.1  |

|        |              |             |       |              |             |      |
|--------|--------------|-------------|-------|--------------|-------------|------|
| 2008_3 | 86473 (1.9)  | 6144 (0.7)  | -10.4 | 22361 (0.7)  | 5531 (0.8)  | 0.1  |
| 2008_4 | 87084 (1.9)  | 6544 (0.7)  | -10.0 | 24204 (0.8)  | 5940 (0.8)  | 0.0  |
| 2009_1 | 95519 (2.1)  | 7796 (0.9)  | -9.8  | 29130 (1.0)  | 7187 (1.0)  | 0.0  |
| 2009_2 | 94537 (2.0)  | 8004 (0.9)  | -9.5  | 29934 (1.0)  | 7360 (1.0)  | 0.0  |
| 2009_3 | 94850 (2.0)  | 8223 (0.9)  | -9.3  | 30789 (1.0)  | 7635 (1.0)  | 0.1  |
| 2009_4 | 96208 (2.1)  | 8485 (1.0)  | -9.2  | 31923 (1.1)  | 7898 (1.1)  | 0.1  |
| 2010_1 | 110148 (2.4) | 10062 (1.1) | -9.5  | 38170 (1.3)  | 9356 (1.3)  | 0.0  |
| 2010_2 | 109017 (2.3) | 10314 (1.2) | -9.1  | 39110 (1.3)  | 9633 (1.3)  | 0.0  |
| 2010_3 | 108572 (2.3) | 10551 (1.2) | -8.8  | 40100 (1.3)  | 9799 (1.3)  | -0.1 |
| 2010_4 | 113821 (2.4) | 11620 (1.3) | -8.4  | 44426 (1.5)  | 10891 (1.5) | 0.0  |
| 2011_1 | 129155 (2.8) | 13725 (1.5) | -8.5  | 52615 (1.8)  | 12850 (1.7) | -0.1 |
| 2011_2 | 125736 (2.7) | 14025 (1.6) | -7.8  | 53719 (1.8)  | 13165 (1.8) | 0.0  |
| 2011_3 | 123703 (2.7) | 14205 (1.6) | -7.4  | 54494 (1.8)  | 13359 (1.8) | 0.0  |
| 2011_4 | 124653 (2.7) | 15333 (1.7) | -6.5  | 59000 (2.0)  | 14431 (2.0) | -0.1 |
| 2012_1 | 131380 (2.8) | 17910 (2.0) | -5.3  | 69442 (2.3)  | 16849 (2.3) | -0.2 |
| 2012_2 | 126418 (2.7) | 18198 (2.0) | -4.4  | 70033 (2.3)  | 17085 (2.3) | -0.1 |
| 2012_3 | 121260 (2.6) | 18078 (2.0) | -3.9  | 69070 (2.3)  | 16918 (2.3) | 0.0  |
| 2012_4 | 131044 (2.8) | 20429 (2.3) | -3.3  | 78666 (2.6)  | 19184 (2.6) | -0.1 |
| 2013_1 | 130151 (2.8) | 21373 (2.4) | -2.5  | 82260 (2.7)  | 19967 (2.7) | -0.2 |
| 2013_2 | 128533 (2.8) | 21764 (2.4) | -2.0  | 83364 (2.8)  | 20133 (2.7) | -0.3 |
| 2013_3 | 124371 (2.7) | 22281 (2.5) | -1.1  | 84688 (2.8)  | 20487 (2.8) | -0.3 |
| 2013_4 | 128761 (2.8) | 24688 (2.8) | 0.0   | 93722 (3.1)  | 22651 (3.1) | -0.3 |
| 2014_1 | 128139 (2.8) | 26430 (3.0) | 1.3   | 98102 (3.3)  | 23829 (3.2) | -0.2 |
| 2014_2 | 127854 (2.7) | 27648 (3.1) | 2.1   | 101096 (3.4) | 24604 (3.3) | -0.2 |
| 2014_3 | 127506 (2.7) | 28263 (3.2) | 2.5   | 102538 (3.4) | 24939 (3.4) | -0.2 |
| 2014_4 | 130646 (2.8) | 30883 (3.5) | 3.8   | 111401 (3.7) | 27120 (3.7) | -0.2 |
| 2015_1 | 130571 (2.8) | 31491 (3.5) | 4.1   | 112469 (3.7) | 27423 (3.7) | -0.1 |
| 2015_2 | 127994 (2.7) | 31904 (3.6) | 4.7   | 112165 (3.7) | 27342 (3.7) | -0.1 |
| 2015_3 | 124661 (2.7) | 33428 (3.7) | 6.1   | 113455 (3.8) | 27891 (3.8) | 0.0  |
| 2015_4 | 121914 (2.6) | 37600 (4.2) | 8.8   | 122826 (4.1) | 30306 (4.1) | 0.1  |
| 2016_1 | 121293 (2.6) | 38767 (4.3) | 9.5   | 124620 (4.2) | 30641 (4.2) | 0.0  |
| 2016_2 | 117894 (2.5) | 38579 (4.3) | 9.9   | 121443 (4.0) | 29917 (4.1) | 0.1  |
| 2016_3 | 113004 (2.4) | 38675 (4.3) | 10.6  | 117449 (3.9) | 29033 (3.9) | 0.1  |
| 2016_4 | 116529 (2.5) | 41911 (4.7) | 11.8  | 125101 (4.2) | 30947 (4.2) | 0.2  |
| 2017_1 | 108139 (2.3) | 42658 (4.8) | 13.3  | 116424 (3.9) | 29301 (4.0) | 0.5  |
| 2017_2 | 100572 (2.2) | 42523 (4.8) | 14.3  | 105167 (3.5) | 26606 (3.6) | 0.6  |
| 2017_3 | 87684 (1.9)  | 38239 (4.3) | 13.9  | 89045 (3.0)  | 22305 (3.0) | 0.3  |
| 2017_4 | 79599 (1.7)  | 36463 (4.1) | 14.2  | 85675 (2.9)  | 21240 (2.9) | 0.2  |

| Admission Season   |               |               |      |               |               |      |
|--------------------|---------------|---------------|------|---------------|---------------|------|
| December - January | 800763 (17.2) | 148980 (16.7) | -1.4 | 507743 (16.9) | 124583 (16.9) | 0.0  |
| June - July        | 761248 (16.4) | 146150 (16.4) | 0.1  | 491069 (16.4) | 120442 (16.3) | -0.1 |

Abbreviations: COPD, chronic obstructive pulmonary disease; LOS, length of stay; MMEs, morphine milligram equivalents; NSAIDs, nonsteroidal anti-inflammatory drugs; std diff, standardized difference

**eTable 4. Variables Measured Following Exposure Group Assignment**

| Characteristic                                          | Opioids only        | Gabapentinoids + opioids |
|---------------------------------------------------------|---------------------|--------------------------|
|                                                         | N = 3,002,480       | N = 737,383              |
| Post-procedure length of stay (including procedure day) |                     |                          |
| mean (SD), days                                         | 3.9 (2.4)           | 3.9 (2.2)                |
| median (IQR), days                                      | 4 (3 – 4)           | 4 (3 – 4)                |
| Total MMEs dispensed on postoperative day 1             |                     |                          |
| mean (SD)                                               | 88.4 (113.3)        | 85.3 (113.7)             |
| median (IQR)                                            | 58.5 (25.0 – 105.0) | 52.5 (22.5 – 100.0)      |

IQR, interquartile range, 25<sup>th</sup> – 75<sup>th</sup> percentile; MMEs, morphine milligram equivalents; SD, standard deviation  
Characteristics were assessed in the PS-weighted study population but were not included in the PS estimation.

**eTable 5. Unadjusted Associations Between Exposure to Gabapentinoids and Opioids and Opioid-Related Adverse Events in the Overall Population**

|                                        | Opioids only             | Gabapentinoids +<br>with opioids | Hazard Ratios<br>(95% CIs) |
|----------------------------------------|--------------------------|----------------------------------|----------------------------|
| <b>Outcomes</b>                        | N = 4,655,183            | N = 892,484                      |                            |
| <i>Primary outcome</i>                 | <i>No. of Events (%)</i> |                                  |                            |
| Overdose                               | 318 (0.007)              | 123 (0.014)                      | 2.22 (1.80 - 2.73)         |
| <i>Secondary outcomes</i>              |                          |                                  |                            |
| Respiratory complications              | 12,674 (0.27)            | 2,503 (0.28)                     | 1.18 (1.13 - 1.23)         |
| Unspecified adverse effects of opioids | 3,080 (0.07)             | 1,027 (0.12)                     | 1.93 (1.80 - 2.07)         |
| Composite outcome                      | 14,787 (0.32)            | 3,187 (0.36)                     | 1.28 (1.23 - 1.33)         |

CI denotes confidence interval. Composite outcome included opioid overdose, respiratory complications, or unspecified adverse effects of opioids.

**eTable 6. Primary and Sensitivity Analyses for Secondary Outcomes**

| <b>Outcome /Analysis</b>                        | <b>Adjusted Hazard Ratios<br/>(95% CI)</b> |
|-------------------------------------------------|--------------------------------------------|
| <b>Respiratory complications</b>                |                                            |
| Primary analysis <sup>a</sup>                   | 1.68 (1.59-1.78)                           |
| Intention-to-treat                              | 1.56 (1.48-1.65)                           |
| No exposure carry-over <sup>b</sup>             | 1.63 (1.54-1.73)                           |
| Follow-up from postoperative day 1 <sup>c</sup> | 2.08 (1.92-2.25)                           |
| <b>Unspecified adverse effects of opioids</b>   |                                            |
| Primary analysis <sup>a</sup>                   | 1.77 (1.61-1.93)                           |
| Intention-to-treat                              | 1.62 (1.48-1.76)                           |
| No exposure carry-over <sup>b</sup>             | 1.74 (1.58-1.92)                           |
| Follow-up from postoperative day 1 <sup>c</sup> | 2.36 (2.09-2.67)                           |
| <b>Composite outcome</b>                        |                                            |
| Primary analysis <sup>a</sup>                   | 1.70 (1.62-1.79)                           |
| Intention-to-treat                              | 1.57 (1.50-1.65)                           |
| No exposure carry-over <sup>b</sup>             | 1.66 (1.57-1.75)                           |
| Follow-up from postoperative day 1 <sup>c</sup> | 2.15 (2.00-2.30)                           |

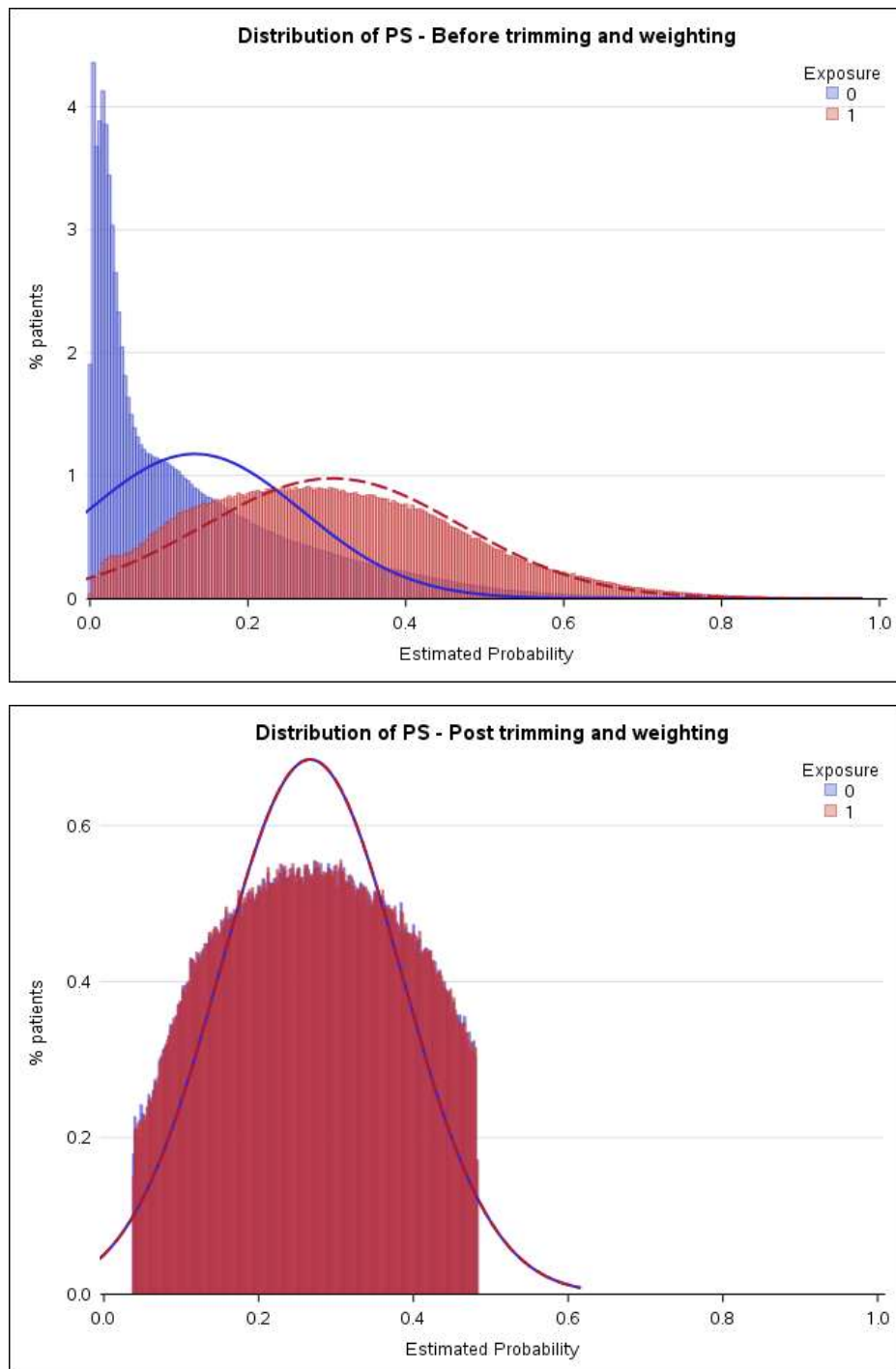
CI denotes confidence interval

<sup>a</sup> Follow-up started on the day of surgery, patients were considered exposed on the day of and through the day following a treatment charge and were censored on deviation from the initial treatment regimen.

<sup>b</sup> Patients were considered exposed only on the day of a treatment charge.

<sup>c</sup> Follow-up started on postoperative day 1. Patients with naloxone charge on the day of surgery were excluded; propensity scores were re-estimated and the population was re-weighted.

**eFigure 1. Propensity Score Distribution Before and After Trimming and Weighting**

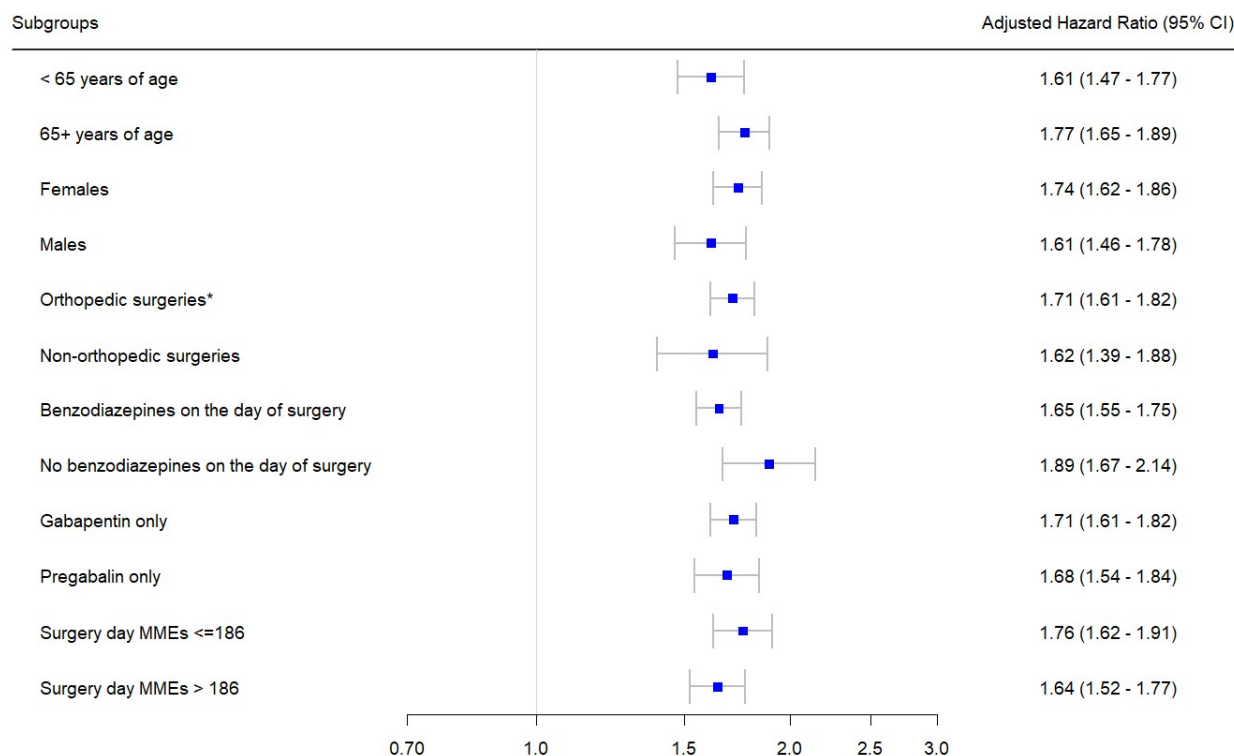


Exposure: 0 – opioids only; 1 – gabapentinoids + opioids; PS – propensity score

Number of patients trimmed with PS  $\leq$  2.5<sup>th</sup> percentile in the gabapentinoid-exposed: 1,536,324 opioids-only patients and 22,312 patients on gabapentinoids + opioids.

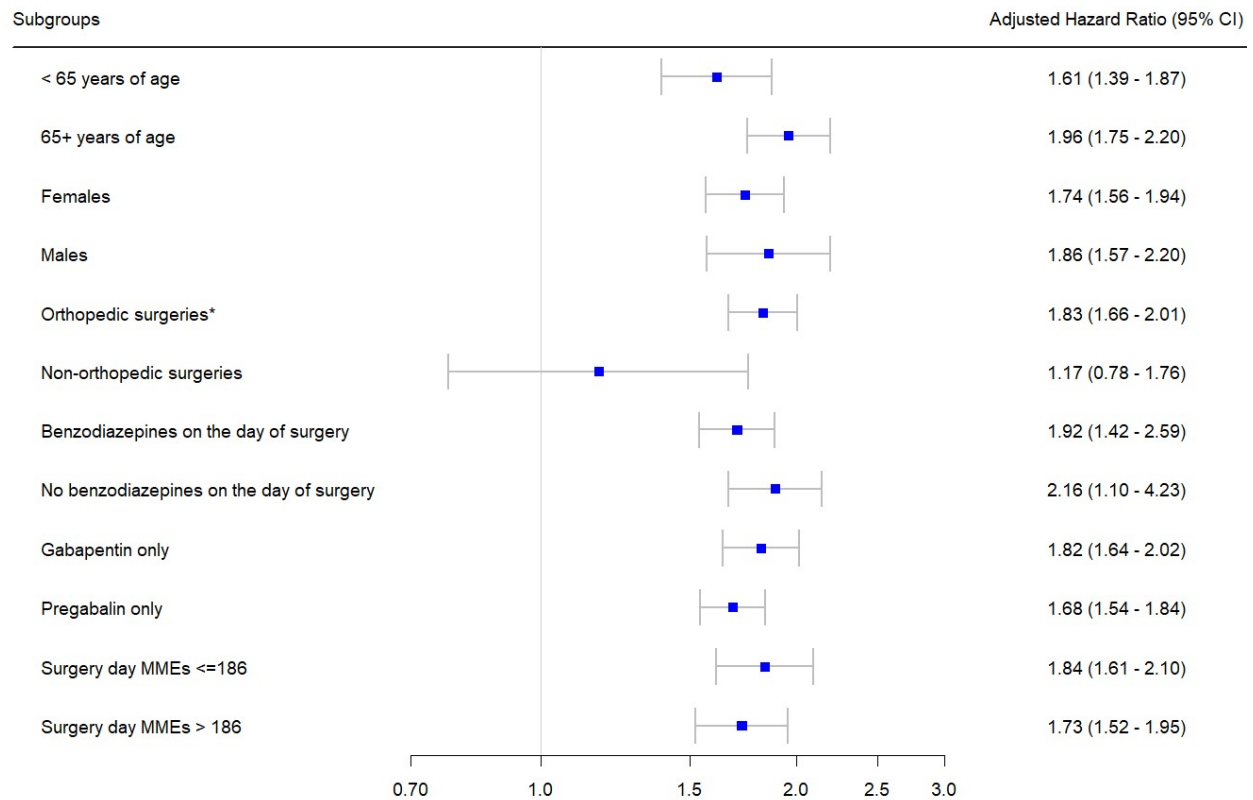
Number of patients trimmed with PS  $\geq$  97.5<sup>th</sup> percentile in the reference group (opioids only): 116,379 opioids-only patients and 132,789 patients on gabapentinoids + opioids.

## eFigure 2. Associations Between Exposure to Gabapentinoids and Opioids and the Outcome of Respiratory Complications Among Subgroups



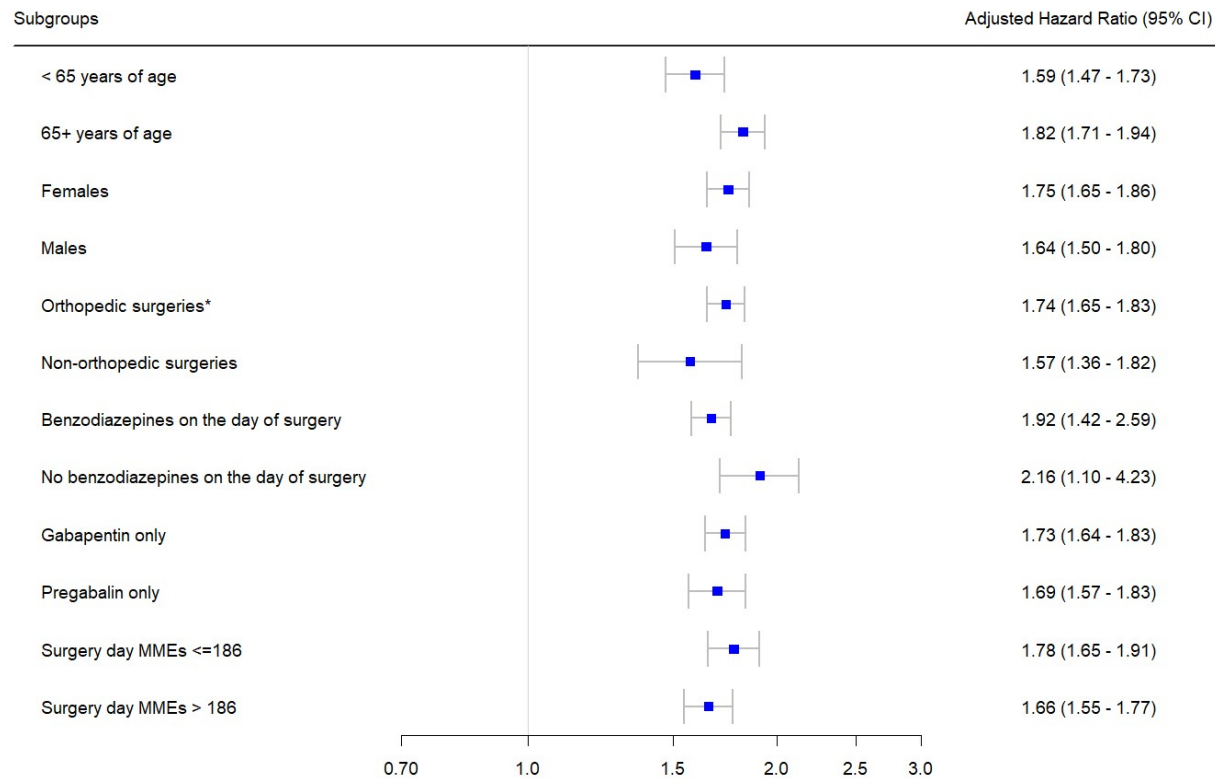
\*orthopedic surgeries included hip arthroplasty, knee arthroplasty, laminectomy or spinal fusion, and a surgery for hip fracture or dislocation. MMEs denote morphine milligram equivalents.

**eFigure 3. Associations Between Exposure to Gabapentinoids and Opioids and the Outcome of Unspecified Adverse Effects of Opioids Among Subgroups**



\*orthopedic surgeries included hip arthroplasty, knee arthroplasty, laminectomy or spinal fusion, and a surgery for hip fracture or dislocation. MMEs denote morphine milligram equivalents.

# eFigure 4. Associations Between Exposure to Gabapentinoids and Opioids and the Composite Outcome of Overdose, Respiratory Complications, and Unspecified Adverse Effects of Opioids Among Subgroups



\*orthopedic surgeries included hip arthroplasty, knee arthroplasty, laminectomy or spinal fusion, and a surgery for hip fracture or dislocation. MMEs denote morphine milligram equivalents.