**Supporting Information**

Figure S1. The use of tramadol according to data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) between 2002 and 2015.

Table S1. Classification of drugs and diseases based on the Anatomical Therapeutic Chemical (ATC) Classification System and 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10), respectively.

**Method S1.** Nested case-control approach.

Table S2. Characteristics of the study population during the risk and reference period, respectively.

Table S3. Subgroup analysis of seizure risk associated with the use of tramadol.

**Table S4.** Sensitivity analysis of the window period and lag time durations between case and future case.

**Figure S2.** Flow chart for the nested case-control approach.

**Table S5.** Baseline characteristics of cases and matched controls in the nested case-control approach.

**Table S6.** Crude and adjusted odds ratios of seizure events associated with tramadol use in the nested case-control approach.

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Figure S1. The use of tramadol according to data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) between 2002 and 2015.

Table S1. Classification of drugs and diseases based on the Anatomical Therapeutic Chemical (ATC) Classification System and 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10), respectively.

|  |  |
| --- | --- |
| **Diagnosis or drug** | **ICD-10 or ATC codes** |
| **Study drug (ATC codes)** |  |
| Tramadol | N02AX02 |
| **Study outcomes (ICD-10 or ATC codes)** | |
| Seizure | G40, G41, F80.3, and R56 |
| Antiepileptic drugs | N03A |
| **Medical history, pain, or pain-related events (ICD-10 codes)** | |
| Diabetes | E10-E14 |
| Cardiovascular disease | I10-I15, I20-I25, I50, I60-I66, and G45 |
| Chronic kidney disease | N18 and N19 |
| Chronic obstructive pulmonary disease | J43.1, J43.2, J43.8, J43.9, and J44 |
| Liver disease | K70-K77 |
| Headache | R51, G43, and G44 |
| Neuralgia | G50.0, G53.0, B02.2, and M79.2 |
| Abdominal and pelvic pain | R10 |
| Chest pain | R07 |
| Musculoskeletal pain | G56, G57, G58, G72, L40.5, M02, M07-M25, M43, M45-54, M60, M62, M63, M65-M68, M70-M72, M75-M77, M79.1, M79.6, M79.7, M80, M84, M89, M04, and M99 |
| Other pain | R52 |
| Injury or trauma | S02, S06, S12, S22, S32, S42, S52, S62, S72, S82, S92, V, W, X, and Y |
| **Co-medications (ATC codes)** | |
| Acetaminophen | N02BE01 |
| NSAIDs | N02BA01 and M01A |
| Opioid analgesics (Excl. tramadol) | N02A (excl. N02AX02) |
| Antidepressants | N06A |
| SSRI | N06AB |
| SNRI | N06AX16, N06A17, N06AX21, and N06AX23 |
| TCA | N06AA02, N06AA04, N06AA09, N06AA12, N06AA16, N06AA17, N06AA21, and N06AA23 |
| Benzodiazepine | N03AE, N05BA, and N05CD |
| Z-drug | N05CF02 and N05CF01 |
| Antipsychotics | N05A |
| **Abbreviations:** ATC, anatomical therapeutic chemical classification system; ICD-10, 10th revision of the International Classification of Diseases and Related Health Problems; NSAIDs, non-steroidal anti-inflammatory drugs; SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants | |

**Method S1.** Nested case-control approach

***Study population***

We collated a population-based cohort of patients from the 2006 National Health Insurance Service-National Sample Cohort (NHIS-NSC) database. Cohort entry was defined as January 1, 2007, for all patients. At cohort entry, patients were required to have at least 1 year of baseline medical history in the NHIS-NSC. We excluded patients with a history of seizure events (defined in the Methods section) in the year before cohort entry and those who had been diagnosed with cancer at any time during the study period. Patient follow-ups were performed from cohort entry until a seizure event, death from any cause, or the end of the study period (December 31, 2015).

***Case-control selection***

A nested case-control analysis was conducted within the cohort. All patients experienced a seizure event during the follow-up period. The index date was defined as the date of first seizure. Two controls were randomly selected from the risk sets of each case and matched for age, sex, and follow-up duration. The index date of the controls was defined as the index date of the matched case.

***Exposure definition***

Cases and controls were classified into two mutually exclusive categories by their exposure status at the index date: (1) tramadol use 30 d before the index date, defined by a prescription and the number of days supplied, and (2) no use of tramadol 30 d before the index date.

***Statistical analysis***

Descriptive statistics were used to summarize the baseline characteristics of the patients and matched controls. We used logistic regression to estimate the odds ratios (ORs) with 95% confidence intervals (CIs) of seizures and compared tramadol use with non-use. The covariates in the regression model were similar to those considered in the case–case-time-control approach. Age and sex were assessed at the date of cohort entry; the other variables were assessed within 1 year before the cohort entry date.

Table S2. Characteristics of the study population during the risk and reference period, respectively.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cases (n = 2,523)** | | | | | |  | **Controls from future cases (n = 2,523)** | | | | | | |
| **Characteristics, N(%)** | **Risk period** | | **Reference period 1** | | **Reference period 2** | |  | | **Risk  period** | | **Reference period 1** | | **Reference period 2** | |
| **Co-medications** |  |  |  |  |  |  |  | |  |  |  |  |  |  |
| Acetaminophen | 595 | (23.6) | 472 | (18.7) | 454 | (18.0) |  | | 399 | (15.8) | 422 | (16.7) | 414 | (16.4) |
| NSAIDs | 837 | (33.2) | 745 | (29.5) | 725 | (28.7) |  | | 659 | (26.1) | 663 | (26.3) | 649 | (25.7) |
| Other opioid analgesics | 67 | (2.7) | 44 | (1.7) | 45 | (1.8) |  | | 22 | (0.9) | 31 | (1.2) | 30 | (1.2) |
| Antidepressants | 348 | (13.8) | 270 | (10.7) | 262 | (10.4) |  | | 270 | (10.7) | 255 | (10.1) | 236 | (9.4) |
| SSRI | 162 | (6.4) | 121 | (4.8) | 115 | (4.6) |  | | 128 | (5.1) | 113 | (4.5) | 102 | (4.0) |
| SNRI | 27 | (1.1) | 28 | (1.1) | 26 | (1.0) |  | | 17 | (0.7) | 17 | (0.7) | 16 | (0.6) |
| TCA | 141 | (5.6) | 106 | (4.2) | 107 | (4.2) |  | | 104 | (4.1) | 106 | (4.2) | 97 | (3.8) |
| Other antidepressants | 117 | (4.6) | 100 | (4.0) | 96 | (3.8) |  | | 106 | (4.2) | 94 | (3.7) | 86 | (3.4) |
| Benzodiazepines | 708 | (28.1) | 538 | (21.3) | 512 | (20.3) |  | | 475 | (18.8) | 479 | (19.0) | 448 | (17.8) |
| Z-drugs | 126 | (5.0) | 108 | (4.3) | 109 | (4.3) |  | | 87 | (3.4) | 72 | (2.9) | 76 | (3.0) |
| Antipsychotics | 361 | (14.3) | 310 | (12.3) | 311 | (12.3) |  | | 248 | (9.8) | 258 | (10.2) | 240 | (9.5) |
| Comorbidities |  |  |  |  |  |  |  | |  |  |  |  |  |  |
| Headache | 148 | (5.9) | 78 | (3.1) | 65 | (2.6) |  | | 53 | (2.1) | 54 | (2.1) | 66 | (2.6) |
| Neuralgia | 27 | (1.1) | 18 | (0.7) | 15 | (0.6) |  | | 10 | (0.4) | 9 | (0.4) | 5 | (0.2) |
| Abdominal and pelvic pain | 33 | (1.3) | 26 | (1.0) | 35 | (1.4) |  | | 14 | (0.6) | 19 | (0.8) | 20 | (0.8) |
| Chest pain | 20 | (0.8) | 16 | (0.6) | 12 | (0.5) |  | | 22 | (0.9) | 13 | (0.5) | 13 | (0.5) |
| Musculoskeletal pain | 447 | (17.7) | 385 | (15.3) | 377 | (14.9) |  | | 362 | (14.3) | 368 | (14.6) | 367 | (14.5) |
| Other pain | 8 | (0.3) | 4 | (0.2) | 6 | (0.2) |  | | 2 | (0.1) | 1 | (0.0) | 4 | (0.2) |
| Injury or trauma | 118 | (4.7) | 71 | (2.8) | 65 | (2.6) |  | | 51 | (2.0) | 42 | (1.7) | 53 | (2.1) |
| Surgery | 95 | (3.8) | 90 | (3.6) | 78 | (3.1) |  | | 48 | (1.9) | 58 | (2.3) | 56 | (2.2) |
| Abbreviations:NSAIDs, non-steroidal anti-inflammatory drugs; SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants | | | | | | | | | | | | | | |

Table S3. Subgroup analysis of seizure risk associated with the use of tramadol.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Subgroup** | **Exposed in  risk period** | | **Exposed in  reference  period 1** | | Exposed in  reference  period 2 | | **cOR** | **(95% CI)** | **aOR†** | **(95% CI)** |
| **Age <20** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 456) | 46 | (10.09) | 26 | (5.70) | 29 | (6.36) | 1.79 | (1.18–2.73) | 1.33 | (0.84–2.12) |
| Future-case control-crossover (n = 456) | 20 | (4.39) | 23 | (5.04) | 18 | (3.95) | 0.97 | (0.55–1.71) | 1.00 | (0.54–1.85) |
| CCTC | NA |  | NA |  | NA |  | 1.84 | (0.91–3.72) | 1.33 | (0.62–2.87) |
| **Age 20–64** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 1,510) | 216 | (14.30) | 159 | (10.53) | 128 | (8.48) | 1.70 | (1.39–2.08) | 1.12 | (0.87–1.44) |
| Future-case control-crossover (n = 1,510) | 150 | (9.93) | 148 | (9.80) | 139 | (9.21) | 1.06 | (0.85–1.33) | 1.14 | (0.87–1.49) |
| CCTC | NA |  | NA |  | NA |  | 1.60 | (1.18–2.17) | 0.99 | (0.68–1.42) |
| **Age 65+** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 557) | 95 | (17.06) | 77 | (13.82) | 76 | (13.64) | 1.38 | (1.01–1.89) | 1.30 | (0.89–1.89) |
| Future-case control-crossover (n = 557) | 82 | (14.72) | 69 | (12.39) | 59 | (10.59) | 1.47 | (1.04–2.08) | 1.81 | (1.21–2.70) |
| CCTC | NA |  | NA |  | NA |  | 0.94 | (0.59–1.50) | 0.72 | (0.41–1.24) |
| **Male** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 1,261) | 161 | (12.77) | 119 | (9.44) | 97 | (7.69) | 1.64 | (1.30–2.06) | 1.10 | (0.84–1.46) |
| Future-case control-crossover (n = 1,261) | 101 | (8.01) | 104 | (8.25) | 99 | (7.85) | 0.99 | (0.76–1.31) | 1.11 | (0.81–1.52) |
| CCTC | NA |  | NA |  | NA |  | 1.65 | (1.15–2.35) | 1.00 | (0.66–1.52) |
| **Female** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 1,262) | 196 | (15.53) | 143 | (11.33) | 136 | (10.78) | 1.61 | (1.29–2.00) | 1.23 | (0.95–1.58) |
| Future-case control-crossover (n = 1,262) | 151 | (11.97) | 136 | (10.78) | 117 | (9.27) | 1.28 | (1.01–1.63) | 1.42 | (1.08–1.87) |
| CCTC | NA |  | NA |  | NA |  | 1.26 | (0.91–1.74) | 0.86 | (0.59–1.25) |
| **Use of opioids** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 180) | 57 | (31.67) | 49 | (27.22) | 46 | (25.56) | 1.44 | (0.90–2.29) | 0.73 | (0.38–1.38) |
| Future-case control-crossover (n = 180) | 33 | (18.33) | 35 | (19.44) | 33 | (18.33) | 0.92 | (0.46–1.83) | 0.81 | (0.38–1.72) |
| CCTC | NA |  | N/A |  | NA |  | 1.56 | (0.68–3.57) | 0.90 | (0.33–2.41) |
| **No use of opioids** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 2,393) | 426 | (17.80) | 333 | (13.92) | 322 | (13.46) | 1.59 | (1.35–1.88) | 1.22 | (1.01–1.47) |
| Future-case control-crossover (n = 2,393) | 347 | (14.50) | 327 | (13.66) | 345 | (14.42) | 1.06 | (0.89–1.27) | 1.00 | (0.82–1.23) |
| CCTC | NA |  | NA |  | NA |  | 1.50 | (1.18–1.91) | 1.21 | (0.92–1.60) |
| **Use of antidepressants** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 495) | 147 | (29.70) | 125 | (25.25) | 132 | (26.67) | 1.38 | (1.01–1.89) | 1.18 | (0.81–1.72) |
| Future-case control-crossover (n = 495) | 146 | (29.49) | 123 | (24.85) | 131 | (26.46) | 1.47 | (1.05–2.07) | 1.31 | (0.88–1.94) |
| CCTC | NA |  | NA |  | NA |  | 0.94 | (0.59–1.49) | 0.90 | (0.52–1.56) |
| **No use of antidepressants** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 1,971) | 322 | (16.34) | 243 | (12.33) | 228 | (11.57) | 1.67 | (1.39–2.00) | 1.15 | (0.92–1.43) |
| Future-case control-crossover (n = 1,971) | 252 | (12.79) | 248 | (12.58) | 249 | (12.63) | 1.03 | (0.83–1.27) | 1.05 | (0.83–1.33) |
| CCTC | NA |  | NA |  | NA |  | 1.62 | (1.23–2.15) | 1.09 | (0.79–1.50) |
| **Lower average daily dose (≤50 mg)** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 611) | 267 | (43.70) | 195 | (31.91) | 177 | (28.97) | 1.60 | (1.34–1.92) | 1.22 | (0.95–1.56) |
| Future-case control-crossover (n = 611) | 72 | (11.78) | 65 | (10.64) | 56 | (9.17) | 1.28 | (0.90–1.82) | 1.52 | (1.02–2.28) |
| CCTC | NA |  | NA |  | NA |  | 1.25 | (0.84–1.85) | 0.80 | (0.50–1.28) |
| **Higher average daily dose (>50 mg)** |  |  |  |  |  |  |  |  |  |  |
| Case-crossover (n = 184) | 90 | (48.91) | 67 | (36.41) | 50 | (27.17) | 1.83 | (1.32–2.55) | 1.19 | (0.73–1.64) |
| Future-case control-crossover (n = 184) | 21 | (11.41) | 25 | (13.59) | 22 | (11.96) | 0.86 | (0.48–1.55) | 1.29 | (0.63–2.67) |
| CCTC | NA |  | NA |  | NA |  | 2.12 | (1.08–4.15) | 0.92 | (0.41–2.11) |
| †Adjusted for: acetaminophen, NSAIDs, other opioid analgesics, antidepressants, antipsychotics, headache, musculoskeletal pain, and injury or trauma.  **Abbreviations:** CCTC, case–case-time-control; CI, confidence interval; NA, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; cOR, crude odds ratio; aOR, adjusted odds ratio | | | | | | | | | | |

Table S4. Sensitivity analysis of the window period and lag time durations between case and future case.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Analysis** | **Exposed in  risk period** | | | **Exposed in  reference  period 1** | | | | **Exposed in  reference  period 2** | | | **cOR** | **(95% CI)** | **aOR†** | **(95% CI)** |
| **Time window** |  |  | |  | |  | |  | |  |  |  |  |  |
| **5-day** |  |  | |  | |  | |  | |  |  |  |  |  |
| Case-crossover (n = 2,714) | 156 | (5.75) | | 137 | | (5.05) | | 136 | | (5.01) | 1.26 | (0.97–1.63) | 1.04 | (0.78–1.40) |
| Future-case control-crossover (n = 2,714) | 80 | (2.95) | | 78 | | (2.87) | | 79 | | (2.91) | 1.03 | (0.75–1.41) | 1.11 | (0.78–1.58) |
| CCTC | NA |  | | NA | |  | | NA | |  | 1.23 | (0.81–1.85) | 0.94 | (0.59–1.49) |
| **10-day** |  |  | |  | |  | |  | |  |  |  |  |  |
| Case-crossover (n = 2,681) | 203 | (7.57) | | 174 | | (6.49) | | 171 | | (6.38) | 1.27 | (1.03–1.57) | 1.04 | (0.82–1.33) |
| Future-case control-crossover (n = 2,681) | 113 | (4.21) | | 125 | | (4.66) | | 129 | | (4.81) | 0.85 | (0.66–1.10) | 0.89 | (0.67–1.20) |
| CCTC | NA |  | | NA | |  | | NA | |  | 1.49 | (1.07–2.09) | 1.17 | (0.80–1.71) |
| **20-day** |  |  | |  | |  | |  | |  |  |  |  |  |
| Case-crossover (n = 2,599) | 292 | (11.24) | | 226 | | (8.70) | | 207 | | (7.96) | 1.51 | (1.26–1.79) | 1.04 | (0.85–1.27) |
| Future-case control-crossover (n = 2,599) | 194 | (7.46) | | 170 | | (6.54) | | 197 | | (7.58) | 1.07 | (0.88–1.31) | 1.06 | (0.85–1.33) |
| CCTC | NA |  | | NA | |  | | NA | |  | 1.40 | (1.08–1.82) | 0.98 | (0.72–1.33) |
|  |  |  | |  | |  | |  | |  |  |  |  |  |
| **Lag time between case and future case** | | |  | |  | |  | |  | |  |  |  |  |
| **120–240 d** |  |  | |  | |  | |  | |  |  |  |  |  |
| Case-crossover (n = 2,170) | 300 | (13.82) | | 218 | | (10.05) | | 206 | | (9.49) | 1.58 | (1.33–1.87) | 1.17 | (0.95–1.42) |
| Future-case control-crossover (n = 2,170) | 223 | (10.28) | | 218 | | (10.05) | | 194 | | (8.94) | 1.11 | (0.92–1.34) | 1.19 | (0.96–1.48) |
| CCTC | NA |  | | NA | |  | | NA | |  | 1.42 | (1.10–1.83) | 0.98 | (0.73–1.31) |
| †Adjusted for: acetaminophen, NSAIDs, other opioid analgesics, antidepressants, antipsychotics, headache, musculoskeletal pain, and injury or trauma.  **Abbreviations:** CCTC, case–case-time-control; CI, confidence interval; NA, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; cOR, crude odds ratio; aOR, adjusted odds ratio | | | | | | | | | | | | | | |

**Figure S2.** Flow chart for the nested case-control approach.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| National Health Insurance Service-National Sample Cohort database, 2002–2015 (N = 1,108,369) | | | | | | | | | | |
|  | | | | |  | | | | | |
| Individuals with 1 year of observation data from 2006 (N = 1,021,208) | | | | | | | | | | |
|  | |  | | |  | | | |  | |
|  | |  | | |  | **Excluded**  Patients that experienced a seizure within a year before cohort entry (N = 789)  Patients diagnosed with cancer at any time during the study period (N = 77,312) | | | | |
|  | |  | | |  |
|  | |  | | |  | | | |  | |
| Patients that have never experienced a seizure and cancer (N = 943,107) | | | | | | | | | | |
|  | | | | |  | | | | | |
|  |  | | |  | | |  | | |  |
| Patients with a seizure event during 2007 to 2015 (N = 4,014) | | | |  | | | Patients without seizure event from 2007 to 2015 (N = 939,093) | | | |
|  |  | | |  | | |  | | |  |
| **Excluded**  Patients who received tramadol for more than 6 months within a year before the first seizure event (N = 222) | | | |  | | | **Excluded**  Patients who received tramadol for more than 6 months during the study period (N = 57,874) | | | |
|  |  | | |  | | |  | | |  |
| Eligible cases (N = 3,792) | | | |  | | | Eligible controls (N = 881,219) | | | |
|  |  | | |  | | |  | | |  |
|  |  | | 1:2 Matching by  age, sex, and risk-set sampling | | | | |  | |  |
|  | |  | |
|  |  | | |  | | |  | | |  |
| Matched cases (N = 3,792) | | | |  | | | Matched controls (N = 7,584) | | | |

**Table S5.** Baseline characteristics of cases and matched controls in the nested case-control approach.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristics**† | **Categories** | **Case** | | **Controls** | |
| **N** | **(%)** | **N** | **(%)** |
| Total |  | 3,792 |  | 7,584 |  |
| Age (years) | Median (IQR) | 36 | (11–54) | 36 | (11–54) |
|  | <20 | 1,321 | (34.84) | 2,642 | (34.84) |
|  | 20–44 | 1,974 | (52.06) | 3,948 | (52.06) |
|  | 65+ | 497 | (13.11) | 994 | (13.11) |
| Sex | Male | 2,070 | (54.59) | 4,140 | (54.59) |
|  | Female | 1,722 | (45.41) | 3,444 | (45.41) |
| Type of pain and  pain-related events | Headache | 282 | (7.44) | 293 | (3.86) |
| Neuralgia | 74 | (1.95) | 78 | (1.03) |
| Abdominal and pelvic pain | 239 | (6.30) | 362 | (4.77) |
| Chest pain | 86 | (2.27) | 154 | (2.03) |
| Musculoskeletal pain | 1,167 | (30.78) | 1,904 | (25.11) |
| Other pain | 15 | (0.40) | 32 | (0.42) |
| Injury or trauma | 209 | (5.51) | 271 | (3.57) |
| Surgery | 573 | (15.11) | 925 | (12.20) |
| Co-medications | Acetaminophens | 2,191 | (57.78) | 3,926 | (51.77) |
|  | NSAIDs | 2,572 | (67.83) | 4,689 | (61.83) |
|  | Other opioid analgesics | 144 | (3.80) | 180 | (2.37) |
|  | Antidepressants | 333 | (8.78) | 221 | (2.91) |
|  | SSRI | 120 | (3.16) | 45 | (0.59) |
|  | SNRI | 9 | (0.24) | 7 | (0.09) |
|  | TCA | 201 | (5.30) | 148 | (1.95) |
|  | Other antidepressants | 93 | (2.45) | 48 | (0.63) |
|  | Benzodiazepines | 1,088 | (28.69) | 1,302 | (17.17) |
|  | Z-drugs | 129 | (3.40) | 66 | (0.87) |
|  | Antipsychotics | 864 | (22.78) | 1,061 | (13.99) |
| Comorbidity | Diabetes | 247 | (6.51) | 343 | (4.52) |
|  | Cardiovascular disease | 711 | (18.75) | 954 | (12.58) |
|  | Chronic kidney disease | 20 | (0.53) | 15 | (0.20) |
|  | COPD | 43 | (1.13) | 50 | (0.66) |
|  | Liver disease | 240 | (6.33) | 294 | (3.88) |
| † Age and sex were assessed at the cohort entry date; the other variables were assessed within 1 year before the cohort entry date.  Abbreviations: COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants | | | | | |

**Table S6.** Crude and adjusted odds ratios of seizure events associated with tramadol use in the nested case-control approach.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cases**  **(N = 3,792)** | | **Controls**  **(N = 7,584)** | | **cOR†** | **(95% CI)** | **aOR‡** | **(95% CI)** |
| Tramadol use | 350 | (9.23) | 274 | (2.41) | 2.71 | (2.30–3.19) | 2.33 | (1.97–2.76) |
| Non-use | 3,442 | (90.77) | 7,310 | (64.26) | 1.00 | (Reference) | 1.00 | (Reference) |
| †Cases and controls were matched by age, sex, and risk-set sampling.  ‡Adjusted for: acetaminophen, NSAIDs, other opioid analgesics, antidepressants, antipsychotics, headache, musculoskeletal pain, and injury or trauma.  Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; cOR, crude odds ratio; aOR, adjusted odds ratio | | | | | | | | |