Association between tramadol use and seizures: A nationwide case-case-time-control study

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**Running title:** Association between tramadol use and seizures

**Key points**

* The effect of tramadol use on seizures remains unclear.
* Reports have linked tramadol use to seizures with a potential mechanism, though the results between studies are inconsistent.
* We conducted a nationwide case-based analysis that considered control-selection bias and minimized confounding by time-invariant factors.
* We used the case–case-time-control design among case-crossover variants to adjust for bias from time trends of exposure in the case-crossover approach by using future-case control group.
* We could not identify a significant association between transient use of tramadol and incidence of seizures in clinical practice.

# Abstract

**Purpose: Tramadol may lower the seizure threshold; however, there is no conclusive evidence to confirm this. This study aimed to determine** whether the use of tramadol is associated with the occurrence of seizures.

**Methods: We conducted** a case-case-time-control (CCTC) study by identifying patients who had received tramadol and seizure diagnosis in a nationwide healthcare database in South Korea between 2003 and 2015. Each case was matched for age and sex to one future case to adjust for time trends in exposure without selection bias from the use of an external control group. The use of tramadol was assessed during a risk period of 1–30 days, and two reference periods, 61–90 days and 91–120 days, preceding the first diagnosis of seizures. We calculated the adjusted odds ratio (aOR) by dividing the OR in cases (case-crossover) by the OR in future cases (control-crossover). We performed a dose-response analysis using the average daily dose.

**Results: W**e identified 2,523 incident cases with matched future cases (mean age, 45.4 years; 50% men). The aOR for seizure with tramadol use was 0.94 (95% confidence interval [CI], 0.98-1.43) in the CCTC analysis, with a case-crossover OR of 1.19 (0.98-1.43) and control-crossover OR of 1.27 (1.03-1.56). The dose-response analysis showed a similar trend in the main analysis: a low-dose aOR of 0.80 (0.50-1.28) and a high-dose aOR of 0.92 (0.41-2.11).

**Conclusion: We could not identify a significant association between transient use of tramadol and incidence of seizures in clinical practice.**

# Keywords: tramadol, seizure, pharmacoepidemiology, self-controlled design, case-case-time-control

# Introduction

A boxed warning on the risk of seizures was placed on the package insert of tramadol by the United States Food and Drug Administration (US FDA) in the 1990s.1-3 The alert was based on several spontaneous adverse event reports of seizures following the use of tramadol during post-marketing surveillance.4, 5 Although there were insufficient data to conclude that the causal effect of tramadol is associated with the risk of seizures in a large population, concerns were raised based on its mechanism of action: stimulation of the μ-opioid receptor and inhibition of serotonin-norepinephrine reuptake.6 Although the physiological mechanisms support the evidence, correlation cannot be interpreted as causation without due consideration. This evidence gap must be addressed.

In view of this safety issue, observational studies have been conducted to generate real-world evidence, but with limited interpretation. For example, one systematic review suggesting a potential risk association was largely based on cross-sectional studies.7 Moreover, two observational studies showed comparable point estimates for seizure risk in tramadol users compared with those in non-users (RR 3.7 for cohort study; OR 3.9, 95% CI 0.4-39.2 for nested case-control study).8, 9 However, the former study did not control any confounding factors despite significant imbalances in most of the baseline characteristics between the groups,8 and the latter showed inconclusive results with wide confidence intervals.9 Moreover, these results could also be distorted by confounding by indication due to comparison with nonusers. Given the potential bias in previous studies and the necessity for continued drug use to manage acute and chronic pain, further studies are needed to determine the association between tramadol use and incidence of seizures.10, 11

A case-crossover study design can overcome control-selection bias and minimize confounding by time-invariant factors. A case–case-time-control (CCTC) design is an extension of the case-crossover design that addresses potential exposure time-trends.12 The objective of the present study was to examine the association between tramadol and the incidence of seizures using the CCTC study design to address selection bias.

# Methods

## ***Data Source***

This study was conducted using the information from the National Health Insurance Service–National Sample Cohort (NHIS-NSC), a population-based cohort database in South Korea. It includes 1 million people, comprising 2.2% of the total eligible Korean population in 2006, selected via systematic stratified random sampling with proportional allocation within each stratum constructed by age group, sex, income level, and participant’s eligibility status, followed over 13 years from 2002 to 2015.13 All potential personal identifiers in the NHIS-NSC were replaced with a new unidentifiable code representing each individual patient. The database contains sociodemographic and clinical information on medical claims and prescription drug claims from all care settings (inpatient, outpatient, emergency department, nursing home, and hospice). In this database, diagnoses and procedures are coded according to the International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM), and prescriptions for medication are recorded using a domestic coding system corresponding to the active ingredient, dose, route of administration, and dosage form.

## ***Study Design***

CCTC design is an extension of a case-crossover study design that adjusts for time-trend in exposure without selection bias from the use of an external control group. In this design, future cases represent the exposure time-trends of the cases.12, 14 There was a time-trend in exposure in our study in which the number of tramadol prescriptions gradually increased throughout the study period (Figure S1).10 To provide reasonable exposure time-trends, we selected control from the future cases only if the index date of the current case was within 120–365 days prior to actual events (Figure 1).14 Each case was age (±1 year) and sex matched (1:1) to the control selected from eligible future cases on. The index date of the future-case control was the same as that of the matched case.

## ***Study Population and Outcome Definition***

## We identified the patients that were recently diagnosed with seizures and received tramadol prior to incident seizures between January 1, 2003, and December 31, 2015. Incident cases comprised patients diagnosed with epilepsy, status epileptics, acquired aphasia with epilepsy, or convulsions (10th revision of the International Classification of Diseases and Related Health Problems (ICD-10): G40, G41, F80.3, R56) and prescribed antiepileptic drugs (Table S1). This pre-specified algorithm for selection of patients with seizures showed a high positive predictive value (81.0%) in a previous validation study.15 The index date was defined as the date of the first seizure event during the study period. Note that patients were only included in the study group if they did not experience a seizure during the year prior to the index date. In the case-based analyses, chronic exposure itself can lead to bias;16 thus, we excluded patients with long-term tramadol use. One year prior to the index date was divided into 12 consecutive 30-day periods, and those who received tramadol for more than 6 periods were excluded. Moreover, patients with malignancies at any time prior to the index date were excluded (Figure 2).

## ***Exposure Assessment***

Each case and the control from the future case served as their own risk and reference periods. We divided the 120-day pre-index period into four consecutive 30-day periods, with a risk period of days 1–30, washout period of days 31–60, 1st reference period of days 61–90, and 2nd reference period of days 91–120 prior to the index date (Figure 1). The washout period was included to minimize the possibility of carryover effect from the reference period to risk period.17 We assessed tramadol exposure in each time period using the prescription date and duration. Exposure to tramadol in the 30-day risk period prior to the incident seizure was compared with that of two reference periods to assess whether tramadol triggered seizures.

## ***Potential Confounders***

The following within-person time-varying covariates were measured across the exposure periods: type of pain and pain-related events (headache, neuralgia, abdominal and pelvic pain, chest pain, musculoskeletal pain, other unspecified pain, injury or trauma, and surgery) and use of other analgesics, including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, or seizure threshold-lowering drugs (antidepressants, including selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and others).18 For each medication, we assessed exposure in each time period using the prescription date and duration.

## ***Statistical Analysis***

Descriptive statistics were used to summarize the characteristics of the cases, such as age and sex measured at the index date, time-varying covariates, and comorbidities (diabetes, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease [COPD], and liver disease) measured during the year before the index date. The results were expressed as median and interquartile range (IQR) for continuous variables and as frequencies and percentages (%) for categorical variables. To describe the distribution of potential time-varying confounders, we also evaluated the use of prescription drugs and types of pain-related events in each period for cases and future-case controls.

In the main analysis, we compared exposure to tramadol between the risk period and two reference periods using a case-crossover analysis. Data from each patient were handled as if they were from a 1:2 matched case-control stratum and case-crossover estimates were determined in the pooled analysis of patients. Thus, only discordantly exposed patients contributed to the case-crossover analysis.19 In this 1:2 individually matched, case-control study, a method based on conditional maximum likelihood was used:20 odds ratios (ORs, including a 95% confidence interval, CI) for seizures associated with the use of tramadol were calculated using a conditional logistic regression model stratifying each case. The model included the use of acetaminophen, NSAIDs, other opioid analgesics, antidepressants, antipsychotics, headache, musculoskeletal pain, and injury or trauma at each time period to compute the adjusted OR (aOR). The ORs for the CCTC design were determined by dividing the case–crossover ORs by the future-case control-crossover ORs.

Subgroup analysis was conducted by age (<20, 20-64, and 65+ years) and sex. Additionally, we grouped cases by history of use of other opioid analgesics or antidepressants within 1 year prior to the index date. A subgroup analysis of the average daily dose was conducted, in which the study population was described based on: 1) the average daily dose estimated as the total dose of tramadol divided by the total number of days prescribed during the year prior to the index date, 2) the median estimated across all patients, and 3) classification of the study population as higher or lower average daily dose compared to the median. Matching to the future case was conducted again within each subgroup analysis. We conducted two sensitivity analysis. First, we repeated the main analysis by varying the lengths of the risk period and corresponding washout and reference periods; each 30-day period was reduced to 5-, 10-, and 20-day periods. Second, we re-selected controls from future cases by varying the lag time between the current and future cases in the main analysis from 120–365 d to 120–240 d. All analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC, USA).

***Auxiliary Analysis***

We compared the results of the CCTC analysis with an ordinary case-control design. We defined the base cohort of patients as those that did not experience a seizure during the year before the cohort entry date and conducted 1:2 age-, sex-, and risk-set-matched nested case-control analysis. The logistic regression model was used to estimate crude OR (cOR) and aOR (including 95% CI) of seizure events, comparing tramadol use with non-use within the 30 d prior to the index date (additional information is provided in Method S1 of the Supporting Information).

# Results

Among the 2,902 patients who met the eligibility criteria between 2003 and 2015, we identified 2,523 incident cases with matched future cases (Figure 2). The general characteristics of the study population are summarized in Table 1. The median age was 48 years (IQR 29–63), and the three most common types of pain or pain-related events were musculoskeletal pain (51.49%), surgery (25.37%), and headache (18.03%). Regarding the use of seizure threshold-lowering drugs, 305 (12.09%) patients used opioids, 584 (23.15%) used antidepressants, and 899 (35.63%) used antipsychotics within the year before the index date.

Table 2 presents the number of tramadol users during the risk and reference periods. Exposure to tramadol was more frequent in the risk period than in the reference period for both cases (14.15% vs. 10.38% and 9.24%, respectively) and controls from future cases (9.99% vs. 9.51% and 8.56%, respectively). In the case-crossover analysis (cases), the use of tramadol, albeit insignificant, showed an increased likelihood of seizures (aOR, 1.19; 95% CI 0.98–1.43). In the control-crossover analysis (future-case controls), we observed an increased likelihood of seizures (aOR 1.27, 95% CI 1.03–1.56), which implies that the association may have been driven by the background trend of tramadol use. In the CCTC analysis, tramadol use did not increase the likelihood of seizures (aOR, 0.94; 95% CI, 0.71–1.24).

Figure 3 shows the results of subgroup and sensitivity analyses. In the subgroup analysis, no significant associations were observed between seizure risk and age, sex, history of opioid or antidepressant use, and the average daily dose of tramadol. The results of the sensitivity analysis are consistent with the main findings (Tables S3–S4). In the auxiliary analysis, which included 3,792 cases and 7,584 matched controls (Figure S2 and Table S5), a significant association between tramadol use and incidence of seizures was observed using the ordinary case-control design: cOR was 2.71 (95% CI 2.30–3.19) and aOR was 2.33 (95% CI 1.97–2.76) (Table S6).

# Discussion

In this population-based CCTC study, we did not identify any effects of tramadol use on the incidence of seizures; the design also ruled out statistical effects greater than an OR of 1.24. There were no considerable differences between age groups, sex, concomitant use of seizure-lowering drugs, or tramadol doses. We verified the robustness of the study design through sensitivity analysis with varying time windows and comparison with the magnitude of bias inherent in the ordinary case-control analysis.

The risk of seizures associated with tramadol use first appeared in a number of spontaneous reports during post-marketing safety surveillance in the USA, and the risk was logically substantiated by tramadol’s mechanism of action.5 Seizures are broadly characterized by abnormal neuronal excitability in the central nervous system.21 Changes in the levels of glutamate and γ-aminobutyric acid (GABA) disrupt the balance between stimulatory and inhibitory stimuli in the central nervous system, thereby inducing seizures.21-23 Centrally acting drugs, such as opioids, antidepressants, and antipsychotics, influence the levels of these neurotransmitters and are commonly prescribed as seizure threshold-lowering drugs.18 Given its stimulatory effect on μ-opioid receptor and ability to inhibit serotonin and norepinephrine reuptake, tramadol has a hypothetical potential to lower seizure threshold.24 In fact, several lines of evidence support the pro-convulsant effect of tramadol at the supratherapeutic level, but it remains unclear whether clinically prescribed doses could induce seizures.25, 26 Given its relatively weak affinity for the μ-opioid receptor (10-fold less than that of codeine, for example), the transient use of tramadol is unlikely to be associated with the occurrence of seizures.27-29

Several studies have assessed the association between seizures and tramadol use. However, most of the evidence for tramadol-induced seizures was derived from cross-sectional studies that cannot be used to infer causality due to a lack of time sequence.7 Additionally, the findings of a few longitudinal observational studies are inconsistent and controversial.8, 9, 30, 31 In a case-control study, Morrow et al. found that tramadol, compared with codeine, was not associated with the occurrence of seizures (OR, 1.03; 95% CI 0.93–1.15).31 However, these findings may be confounded by tramadol-related indication as a matching factor between cases and controls. Conversely, a cohort study by Gardner et al. reported a 3-fold increase in the risk of seizures with tramadol use vs. non-use; however, there were systematic differences between the groups, including in risk factors for seizures and the use of seizure threshold-lowering drugs, and the prevalence of head injury, stroke, and migraine were more frequent in tramadol users.8 Moreover, their regression model did not consider any potential confounding factors. As in previous studies, most evidence of seizure risk associated with tramadol use is outdated, biased, or generated from inappropriate study designs with small sample sizes. We believe that sufficient efforts were made in the present study to minimize selection and confounding biases.

The advantage of our study lies in the application of the CCTC design to assess the association between tramadol and the occurrence of seizures. The use of the case-crossover-based approach allowed us to minimize the control-selection bias and confounding by unmeasured time-invariant factors, such as genetic polymorphism in the cytochrome P450 2D6 isoenzyme related to tramadol metabolism.19 This is a robust approach to investigating associations between transient exposure and acute outcome events when the probability of transient exposure is stable during study period.19, 32 To control for transient exposure, we excluded frequent and long-term users of tramadol. Moreover, to maintain a stable probability of exposure over time, we evaluated the trends in exposure during the study period. An increasing trend of tramadol use was observed during the study period; thus, we applied the CCTC design among case-crossover variants to address the bias caused by this trend in exposure.12

We recognize some limitations to our study that could help better the designs of future investigations. Prescriptions in the claims database represent only those written by physicians, and information on whether a patient filled a prescription is not available. We were therefore naïve to individual habits regarding drug consumption, especially if the medication was prescribed *pro re nata*. This would overestimate the exposure in both the risk and reference periods, and this nondifferential exposure misclassification could bias the ORs towards no difference in the case-crossover and future-case control-crossover analyses. Some patients may have also been prescribed tramadol for the prodromal symptoms of seizures, such as headaches;33 thus, protopathic bias cannot be eliminated. Finally, because of the observational nature of the study, there was a potential residual or unmeasured confounding bias. We attempted to minimize this bias by using a case-only design and matching with future cases. However, the study design cannot control for other unidentified confounding factors, such as underreported cases of mild disorders (e.g., headaches) or use of over-the-counter drugs (e.g., acetaminophen).

# Conclusions

Our study found no significant association between the transient use of tramadol and the incidence of seizures. The present study emphasizes the effect of confounding factors and selection bias in the accurate interpretation of clinical data. Future population-based studies with appropriate study question can benefit from the robust CCTC design.

# DECLARATIONS

**Conflicts of interest**

The authors declare that they have no conflicts of interest with respect to this research study and paper. Dr. Shin reports the receipt of research funding from the Ministry of Food and Drug Safety, the Ministry of Health and Welfare, the National Research Foundation, and Government-wide R&D Fund for Infectious Disease Research of the Republic of Korea as well as grants from pharmaceutical companies, including Amgen, Dong-A ST, GlaxoSmithKline, Pfizer, and Yungjin, outside the submitted work.

**Availability of data and material**

The data that support the findings of this study were provided by the National Health Insurance Service of South Korea. Due to domestic laws and regulations that prohibit the distribution or release of individual information to the public, the data is not publicly available. However, the will be made available by the authors upon reasonable request and with permission from the National Health Insurance Service of South Korea.

**Author contributions**

Conceptualization and Methodology: SP, HL, and JYS. Data analysis: SP. Writing – original draft: SP and HL. Writing – review and editing: SP, HL, JHK, JYS, and HLJ. All authors have read and approved the final article.

**Ethics approval**

This study was approved by the Institutional Review Board of Sungkyunkwan University (SKKU-IRB-2020-09-007), which waived the requirement for informed consent.

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Table 1. Baseline characteristics of study population.

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Categories** | N | **(%)** |
| Total |  | 2,523 |  |
| Age (years) | Median (IQR) | 48 | (29–63) |
|  | <20 | 456 | (18.07) |
|  | 20–44 | 1,510 | (59.85) |
|  | 65+ | 557 | (22.08) |
| Sex | Male | 1,261 | (49.98) |
|  | Female | 1,262 | (50.02) |
| Type of pain and  pain-related events | Headache | 455 | (18.03) |
| Neuralgia | 106 | (4.20) |
| Abdominal and pelvic pain | 234 | (9.27) |
| Chest pain | 164 | (6.50) |
| Musculoskeletal pain | 1,299 | (51.49) |
| Other pain | 34 | (1.35) |
| Injury or trauma | 344 | (13.63) |
| Surgery | 640 | (25.37) |
| Co-medications | Acetaminophen | 1,772 | (70.23) |
|  | NSAIDs | 2,086 | (82.68) |
|  | Other opioid analgesics | 305 | (12.09) |
|  | Antidepressants | 584 | (23.15) |
|  | SSRI | 266 | (10.54) |
|  | SNRI | 57 | (2.26) |
|  | TCA | 300 | (11.89) |
|  | Other antidepressants | 232 | (9.20) |
|  | Benzodiazepines | 1,280 | (50.73) |
|  | Z-drug | 298 | (11.81) |
|  | Antipsychotics | 899 | (35.63) |
| Comorbidity | Diabetes | 323 | (12.80) |
|  | Cardiovascular disease | 908 | (35.99) |
|  | Chronic kidney disease | 50 | (1.98) |
|  | COPD | 50 | (1.98) |
|  | Liver disease | 275 | (10.90) |
| † Age and sex were assessed at the index date; the other variables were assessed within 1 year before the index date.  Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants | | | |

Table 2. The association between exposure of tramadol and seizure incidence.

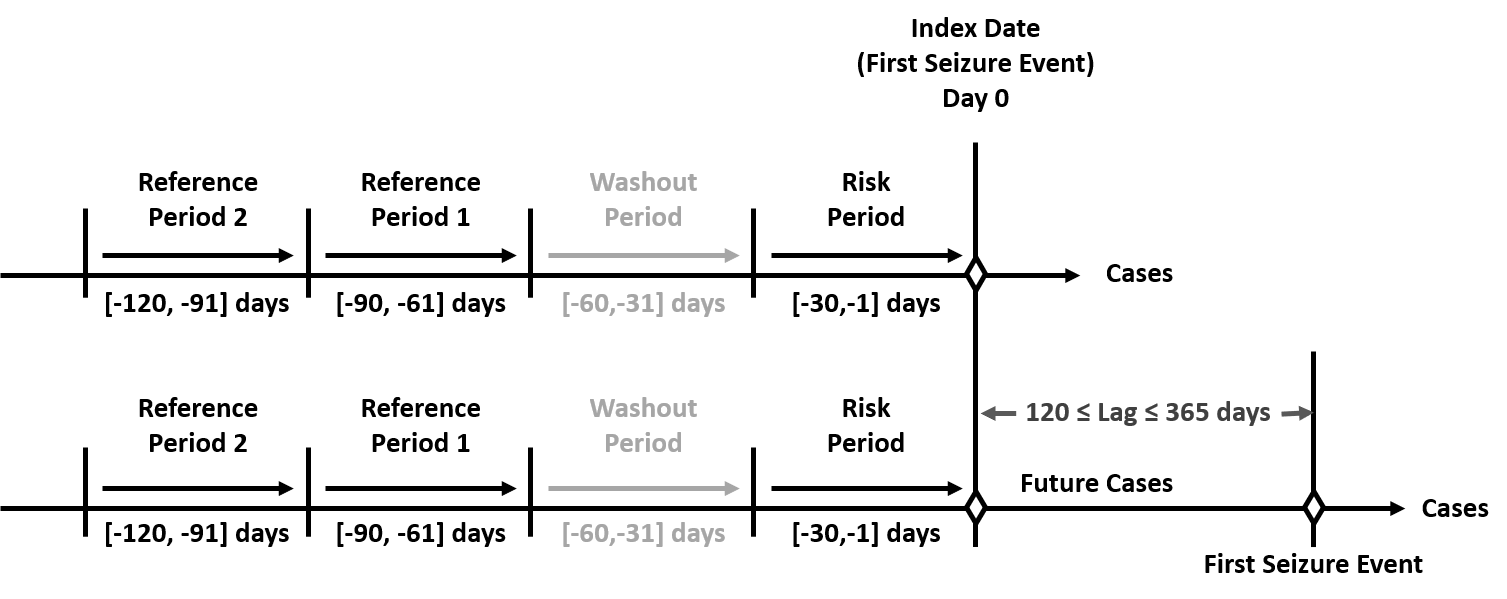
|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **No. patients exposed in  risk period**  **(N = 2,523)** | | **No. patients exposed in  reference period 1**  **(N = 2,523)** | | No. patients exposed in  reference period 2  **(N = 2,523)** | | cOR | **(95% CI)** | aOR† | **(95% CI)** |
| Case-crossover | 357 | (14.15) | 262 | (10.38) | 233 | (9.24) | 1.62 | (1.39–1.90) | 1.19 | (0.98–1.43) |
| Future-case control-crossover | 252 | (9.99) | 240 | (9.51) | 216 | (8.56) | 1.15 | (0.96–1.37) | 1.27 | (1.03–1.56) |
| CCTC | NA |  | NA |  | NA |  | 1.42 | (1.11–1.80) | 0.94 | (0.71–1.24) |
| †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, nonsteroidal anti-inflammatory drugs; cOR, crude odds ratio; aOR, adjusted odds ratio | | | | | | | | | | |

Figure legends

**Figure 1.** Graphical representation of the case–case–time–control design. A seizure event was defined as when a patient was prescribed an antiepileptic drug for epilepsy, status epilepticus, acquired aphasia with epilepsy, or convulsions.

**Figure 2.** Flowchart showing the study population.

**Figure 3.** Forest plot of the association between tramadol use and seizure occurrence in the primary, subgroup, and sensitivity analyses. Odds ratios are derived from the conditional logistic regression analysis of the case–case-time-control models and adjusted for: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), other opioid analgesics, antidepressants, and antipsychotics as well as drugs prescribed for headache, musculoskeletal pain, and injury or trauma. CI, confidence interval; OR, odds ratio



**Figure 1.** Graphical representation of the case–case–time–control design. A seizure event was defined as when a patient was prescribed an antiepileptic drug for epilepsy, status epilepticus, acquired aphasia with epilepsy, or convulsions.

|  |  |  |
| --- | --- | --- |
| National Health Insurance Service-National Sample Cohort database, 2002–2015 (N = 1,108,369) | | |
|  |  | |
| Patients who experienced a seizure and were prescribed anticonvulsants  between January 1, 2003, and December 31, 2015  (N = 7,453) | | |
|  |  | |
|  |  | Excluded  Patients who experienced a seizure within a year before index date (N = 26) |
|  |
|  |  |  |
| Patients that experienced one seizure between January 1, 2003, and December 31, 2015  (N = 7,427) | | |
|  |  |  |
|  |  | Excluded  Patients that have not been prescribed tramadol before the index date (N = 3,575)  Patients diagnosed with cancer prior to index date (N = 397) |
|  |
|  |  |  |
| Patients prescribed tramadol prior to their first seizure (N = 3,178) | | |
|  |  |  |
|  |  | Long-term users of tramadol (N = 276) |
|  |
|  |  |  |
| Patients who transiently used tramadol before their first seizure (N = 2,902) | | |
|  |  |  |
| Patients matched with future case based on age, sex, and calendar time (N = 2,523) | | |

**Figure 2.** Flowchart showing the study population.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Analysis** |  |  | OR | **(95% CI)** | |
| **Primary analysis** |  |  | 0.94 | (0.71–1.24) | |
|  |  |  |  |  | |
| **Subgroup analysis** |  |  |  |  | |
| **Age (in years)** |  |  |  |  | |
| <20 |  |  | 1.33 | (0.62–2.87) | |
| 20–64 |  |  | 0.99 | (0.68–1.42) | |
| ≥65 |  |  | 0.72 | (0.41–1.24) | |
| **Sex** |  |  |  |  | |
| Male |  |  | 1.00 | (0.66–1.52) | |
| Female |  |  | 0.86 | (0.59–1.25) | |
| **Use of opioid analgesics** |  |  |  |  | |
| Yes |  |  | 0.90 | (0.33–2.41) | |
| No |  |  | 1.21 | (0.92–1.60) | |
| **Use of antidepressants** |  |  |  |  | |
| Yes |  |  | 0.90 | (0.52–1.56) | |
| No |  |  | 1.09 | (0.79–1.50) | |
| **Average daily dose** |  |  |  |  | |
| Low |  |  | 0.80 | (0.50–1.28) | |
| High |  |  | 0.92 | (0.41–2.11) | |
|  |  |  |  |  | |
| **Sensitivity analysis** |  |  |  |  | |
| **Time window** |  |  |  |  | |
| 5-day |  |  | 0.94 | (0.59–1.49) | |
| 10-day |  |  | 1.17 | (0.80–1.71) | |
| 20-day |  |  | 0.98 | (0.72–1.33) | |
| **Lag between case and future case** |  |  |  |  | |
| 120–240 d |  |  | 0.98 | (0.73–1.31) | |
|  |  |  |  |  | |
|  | | | | |

**Figure 3.** Forest plot of the association between tramadol use and seizure occurrence in the primary, subgroup, and sensitivity analyses. Odds ratios are derived from the conditional logistic regression analysis of the case–case-time-control models and adjusted for: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), other opioid analgesics, antidepressants, and antipsychotics as well as drugs prescribed for headache, musculoskeletal pain, and injury or trauma. CI, confidence interval; OR, odds ratio