Supplementary Online Content

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

eTable 1. List of opioids other than tramadol and codeine marketed in the United Kingdom

Opioid (active ingredient name)
Alfentanil
Buprenorphine
Dextromoramide
Dextropropoxyphene
Diamorphine
Dipipanone
Ethylmorphine
Fentanyl
Hydromorphone
Levorphanol
Meptazinol
Morphine
Nalbuphine
Naloxone
Oxycodone
Papaveretum
Pentazocine
Pethidine
Phenazocine
Remifentanil
Tapentadol

eTable 2. Baseline characteristics of patients initiating tramadol and codeine for non-cancer pain

Baseline characteristics	Tramadol (n=28,110)	Codeine (n=305,924)
Male, n (%)	12,164 (43.3)	121,419 (39.7)
Age (years), mean (SD)	52.3 (17.8)	50.7 (19.0)
Body mass index, n (%)		
<18.5, kg/m^2	648 (2.3)	7297 (2.4)
18.6-25, kg/m^2	8847 (31.5)	101,139 (33.1)
26-29, kg/m^2	8748 (31.1)	96,119 (31.4)
≥30, kg/m^2	7131 (25.4)	72,332 (23.6)
Unknown	2736 (9.7)	29,037 (9.5)
Smoking status, n (%)		
Ever	14,622 (52.0)	153,427 (50.2)
Never	11,884 (42.3)	131,648 (43.0)
Unknown	1604 (5.7)	20,849 (6.8)
Excessive alcohol use, n (%)	2110 (7.5)	19, 492 (6.4)
Number of general practice visits [a], mean (SD)	19.4 (25.1)	16.6 (21.5)
Number of hospitalizations [a], mean (SD)	0.4 (1.1)	0.2 (0.7)
Number of prescription drugs [b], mean (SD)	7.1 (5.0)	6.2 (4.2)
Comorbidities, n (%)		
Liver disease	2301 (8.2)	16,166 (5.3)
Pancreatic disease	347 (1.2)	1645 (0.5)
Chronic kidney disease	914 (3.3)	7749 (2.5)
Gastric surgery	31 (0.1)	120 (0.0)
Endocrine-related conditions	5 (0.0)	55 (0.0)
Prescription drugs [b], n (%)		
Propoxyphene	2679 (9.5)	18,877 (6.2)
Other opioid analgesics	486 (1.7)	1130 (0.4)
Aspirin	3179 (11.3)	31,116 (10.2)
Non-steroidal anti-inflammatory drugs	3816 (13.6)	38,099 (12.5)
Antidepressants		
Selective serotonin recapture inhibitors	2009 (7.2)	20,032 (6.6)
Serotonin norepinephrine recapture inhibitors	267 (1.0)	2305 (0.8)
Other antidepressants	2200 (7.8)	14,505 (4.7)
Antipsychotics	696 (2.5)	7690 (2.5)
Antiepileptics	942 (3.4)	5986 (2.0)
Antihypertensive drugs, n (%)		
β blockers	2325 (8.3)	23,266 (7.6)
Angiotensin-converting enzyme inhibitors	3048 (10.8)	28,345 (9.3)
Angiotensin receptor blockers	1134 (4.0)	9620 (3.1)
Calcium channel blockers	2514 (8.9)	24,750 (8.1)
Diuretics	2098 (7.5)	23,708 (7.8)
Other antihypertensive drugs	118 (0.4)	977 (0.3)
Antibiotics, n (%)		
Fluoroquinolones	467 (1.7)	2882 (0.9)

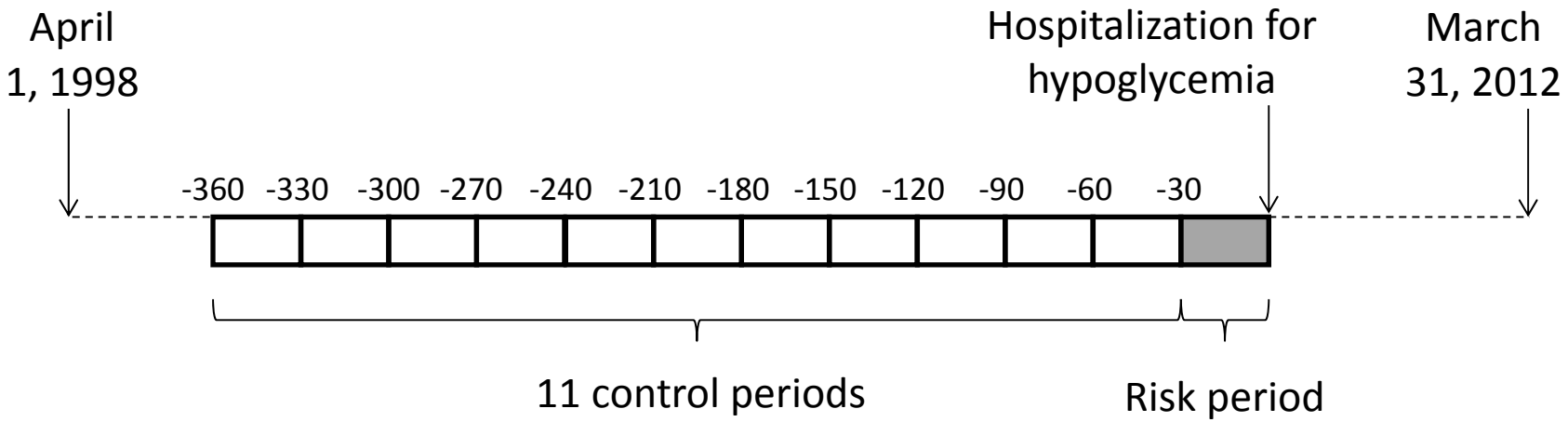
Cotrimoxazole	609 (2.2)	6213 (2.0)
Other antibiotics and combinations	5232 (18.6)	60,787 (19.9)
Anti-diabetic drugs, n (%)		
Insulins	440 (1.6)	4300 (1.4)
Metformin	867 (3.1)	8824 (2.9)
Sulfonylureas	558 (2.0)	5687 (1.9)
Thiazolidinediones	153 (0.5)	1428 (0.5)
Other anti-diabetic drugs	46 (0.2)	537 (0.2)
Type of pain and pain-related events [b], n (%)		
Headache	1065 (3.8)	20,571 (6.7)
Neuralgia	354 (1.3)	1792 (0.6)
Abdominal and pelvic pain	3074 (10.9)	22,850 (7.5)
Musculoskeletal pain	9995 (35.6)	108,108 (35.3)
Other pain	2568 (9.1)	24,044 (7.9)
Injury or trauma	2755 (9.8)	21,131 (6.9)
Surgery	6983 (24.8)	37,628 (12.3)

[a] Measured in the year before cohort entry.
[b] Measured in the 90 days before cohort entry.

eMethods 1. High-dimensional propensity score analysis

The high-dimensional propensity score (HD-PS) analysis is a method that empirically selects covariates based on their prevalence and potential for confounding. Thus, for each patient, we used multivariate logistic regression to calculate a propensity score, which was the probability of being exposed to tramadol oral monotherapy compared with codeine, conditional on 500 empirically identified and 41 predefined covariates measured at cohort entry. The empirical covariates were estimated from seven data dimensions (i. drug prescriptions, ii. procedures, iii. diagnoses, iv. disease history, v. administrative information, and hospitalizations [vi. diagnoses and vii. procedures]), while the 41 predefined covariates consisted of the following variables: calendar year of cohort entry, body mass index, excessive alcohol use (defined as alcohol-related disorders such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic failure), comorbidities previously associated with an increased risk of hypoglycemia (chronic renal insufficiency, liver disease, pancreatic disease, other endocrine disease [including adrenal insufficiency and hypopituitarism], and dumping syndrome-inducing surgeries [gastrectomy and bypass surgery]; all measured in the year prior cohort entry), prescription drugs (insulins, sulfonylureas, metformin, other antidiabetic agents, beta-blockers, angiotensin-converting enzyme inhibitors, fluoroquinolones, cotrimoxazole, antiepileptics, antidepressants, aspirin, non-steroidal anti-inflammatory drugs, dextropropoxyphene, and other opioids; all measured in the 90 days prior to cohort entry), opioid-related indications (headache, abdominal and pelvic pain, musculoskeletal pain, neuralgia, other pain (including chest pain, ear/nose/throat/mouth pain and unspecified pain), injury or trauma, and surgery; all measured in the 90 days prior to cohort entry).

eFigure 1. Graphical representation of the case-crossover design with one risk period and 11 control periods

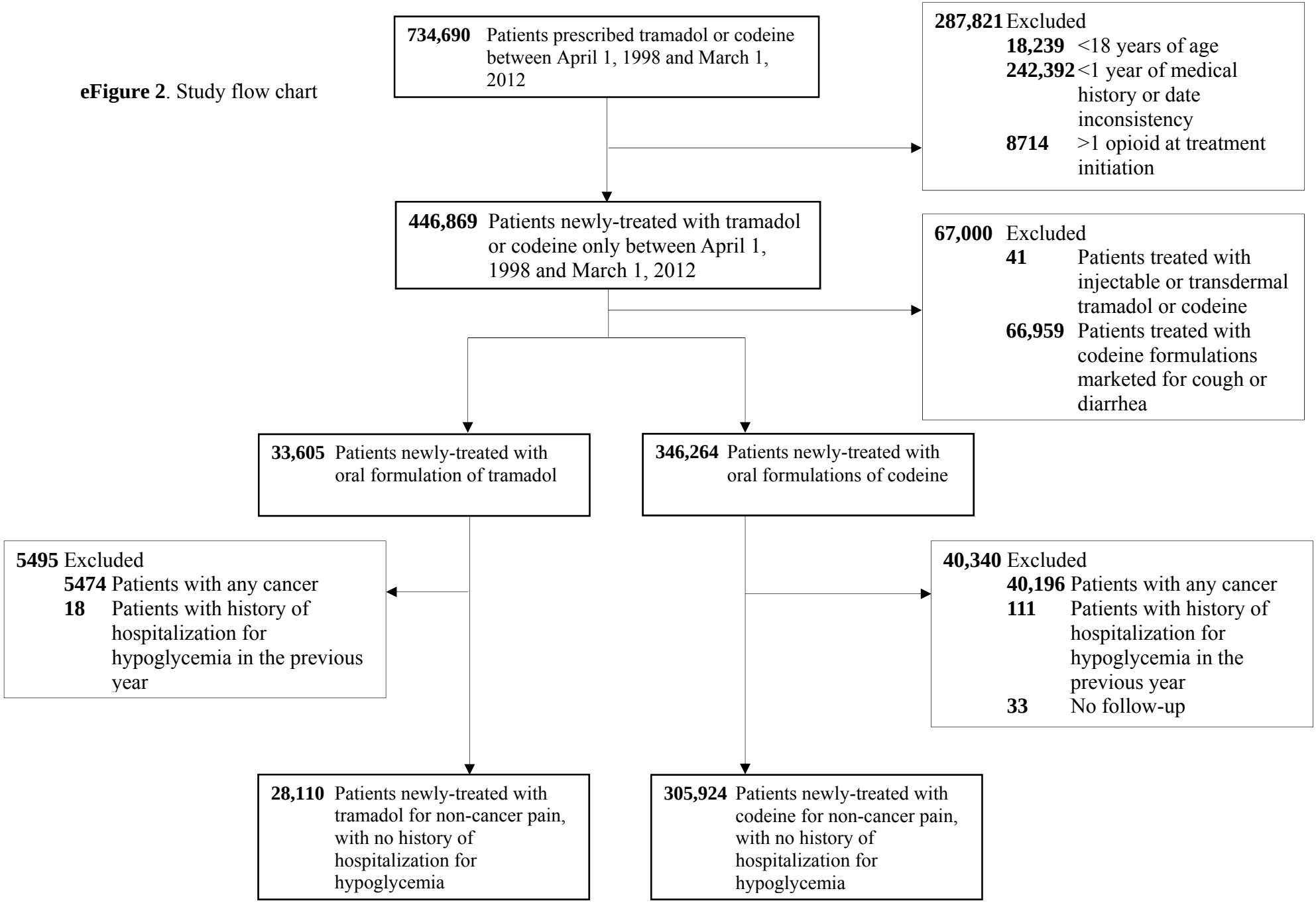


eMethods 2. Exposure time-trend assessment for the case-crossover analysis

One of the assumptions of the case-crossover design is the absence of an exposure time-trend in the case series (Suissa S. The case-time-control design. *Epidemiology*. 1995; 6:248-253). An exposure time-trend could be related to various causes (change in medical practice, new indications for the exposure drug, aggressive marketing). Such time-trends can lead to biased estimates, which may overestimate or underestimate (depending on the direction of the exposure time-trend) the true association between an exposure and outcome. One method to assess the presence of an exposure time-trend is to conduct a control-crossover analysis. Thus, for each case identified in the case-crossover analysis, we selected one control (individual without the event) that was present in the cohort at the time of the case's event date (index date). The case's index date was assigned to that control. A control-crossover was then performed using the exact same time windows as the ones used in the case-crossover method (i.e. one risk period and 11 control periods, all 30 days in length). In the absence of the outcome, the control-crossover odds ratio [OR] is an estimate of any exposure time-trend, with an OR of 1.00 suggesting the absence of an exposure-time trend.

In the present study, the control-crossover OR (95% confidence interval) was 0.96 (0.56-1.63), suggesting no evidence of an exposure time-trend, and thus satisfying a key assumption of the case-crossover design.

eFigure 2. Study flow chart



eTable 3. Crude and adjusted hazard ratios of hospitalization for hypoglycemia associated with tramadol, compared with codeine, in the first 30 days after treatment initiation among patients with non-cancer pain

Exposure	No. of patients	No. of events	Person-months	Incidence rate (per 10,000 person-months)	Crude HR	Adjusted HR (95% CI) [a]
Codeine	305,862	21	295,290	0.7 (0.4-1.1)	1.00	1.00 (Reference)
Tramadol	28,109	8	26,483	3.0 (1.3-6.0)	4.23	3.60 (1.56-8.34)

Abbreviation: HR, hazard ratio; 95% CI, 95% confidence interval
[a] Adjusted for high-dimensional propensity score quartiles.
Note: 2 patients in the tramadol group and 62 in the codeine group were excluded from this analysis due to non-overlapping propensity scores.

eFigure 3. Case-crossover flowchart