

Initial opioid prescription characteristics and risk of opioid misuse, poisoning and dependence: retrospective cohort study.

Supplementary Material

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Table S1. International Classification of Diseases (ICD) and Anatomical Therapeutic Chemical (ATC) codes used for covariates, outcomes, and drugs included in the study.**ATC codes used for medication**

Opioids	N02A, except N02AB02 (petidine), N02AX02 (pentazocine)
Benzodiazepines	N05BA, N05CD, N05CF
Gabapentinoids	N03AX
Antipsychotics	N05A

ICD codes used for comorbidities	International Classification of Disease, 9th edition, ICD-9-CM	International Classification of Disease, 10th edition, ICD-10
Heart failure	428.xx, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.03, 404.13, 404.91, 404.93, 425.4x	I50.x, I11.0, I13.0, I13.2, I42.0
Hypertension	401.xx- 405.xx, 437.2x	I10.x, I11.x, I12.x, I13.x, I15.x, I67.4
Ischemic cardiopathy	410.xx, 411.xx, 412.xx, 413.xx, 414.xx	I20.x, I21.x, I22.x, I23.x, I24.x, I25.x
CODP	491.xx, 492.xx, 496.xx, 493.20, 493.21, 493.22	J41.0, J41.1, J41.9, J42.x, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.8, J44.9
Diabetes	249.xx, 250.xx, 648.0	E08.x- E11.x, E13.x
Renal disease	403.xx, 404.xx, 580.xx- 589.xx, 590.1, 792.5, 753.x, V42.0, V45.1, V56.xx	I12.x, I13.x, N00.x- N05.x, N07.x, N11.x, N14.x, N17.x-N19.x, Q61.x, Z49.x, Z94.0, Z99.2, Z91.15
Liver disease	070.0, 070.2x, 070.4x, 070.6x, 070.71, 570.xx- 573.xx 782.4, 789.1, 789.5, 790.4, 790.5, 794.8, V42.7	B150.x, B160.x, B162.x, B190.x, K70.x- K77.x I85.x, R94.5, Z94.4 R17.x, R18.x, R74.x
Dementia	290.xx, 294.xx, 330.xx, 331.xx	F00.x, F01.x, F02.x, F03.x, G30.x, G31.x
Depression	296.2x, 296.3x, 298.0x, 300.4x, 301.12, 311.xx	F32.x, F33.x, F34.1
Alcohol	291.xx, 303.xx, 305.0x, 980.0, 357.5	E52.x, F10.x, G31.2, G62.1, G72.1, I42.6, K29.2, K70.x, K86.0, O35.4, T51.x, Z71.4
Tobacco	305.1x, 989.84, V15.82	F17.x, T65.2

ICD codes used for outcomes of misuse, poisoning and dependence

965.00, 965.01, 965.02, 965.09, E850.0, E850.1, E850.2, 304.0x, 304.7x, 305.5x	T40.0x, T40.1x, T40.2x, T40.3x, T40.4x, F11.1x, F11.2x, F11.9x
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ICD codes used to identify patients with cancer and prescriptions for cancer conditions

140.* , 141.* , 142.* , 143.* , 144.* ,
145.* , 146.* , 147.* , 148.* , 149.* ,
150.* , 151.* , 152.* , 153.* , 154.* ,
155.* , 156.* , 157.* , 158.* , 159.* ,
160.* , 161.* , 162.* , 163.* , 164.* ,
165.* , 170.* , 171.* , 172.* , 173.* ,
174.* , 175.* , 176.3 , 176.4 , 177.* ,
178.* , 179.* , 180.* , 181.* , 182.* ,
183.* , 184.* , 185.* , 186.* , 187.* ,
188.* , 189.* , 190.* , 191.* , 192.* , 193.* , C00-C96
194.* , 195.* , 196.* , 197.* , 198.* ,
199.* , 200.* , 201.* , 202.* , 203.* ,
204.* , 205.* , 206.* , 207.* , 208.* ,
209.* , 218.* , 235.* , 236.* , 237.* ,
238.* , 239.* , 258.01 , 258.02 , 338.3 ,
357.3 , 528.01 , V10.* , V58.0 , V58.1* ,
990

ICD: International Classification of Diseases ; ATC: Anatomical Therapeutic Chemical: COPD: Chronic obstructive pulmonary disease.

Table S2. Identification of surgical procedures via International Classification of Diseases (ICD) codes.

International Classification of Disease, 9th edition, ICD-9-CM procedures	International Classification of Disease, 9th edition, ICD-9-CM procedures
00 Procedures and interventions, not elsewhere classified	00 Central Nervous System and Cranial Nerves
01-05 Operations on the nervous system	01 Peripheral Nervous System
06-07 Operations on the endocrine system	02 Heart and Great Vessels
08-16 Operations on the eye	03 Upper Arteries
18-20 Operations on the ear	04 Lower Arteries
21-29 Operations on the nose, mouth, and pharynx	05 Upper Veins
30-34 Operations on the respiratory system	06 Lower Veins
35-39 Operations on the cardiovascular system	07 Lymphatic and Hemic Systems
40-41 Operations on the hemic and lymphatic system	08 Eye
42-54 Operations on the digestive system	09 Ear, Nose, Sinus
55-59 Operations on the urinary system	0B Respiratory System
60-64 Operations on the male genital organs	0C Mouth and Throat
65-71 Operations on the female genital organs	0D Gastrointestinal System
76-84 Operations on the musculoskeletal system	0F Hepatobiliary System and Pancreas
85-86 Operations on the integumentary system	0G Endocrine System
	0H Skin and Breast
	0J Subcutaneous Tissue and Fascia
	0K Muscles
	0L Tendons
	0M Bursae and Ligaments
	0N Head and Facial Bones
	0P Upper Bones
	0Q Lower Bones
	0R Upper Joints
	0S Lower Joints
	0T Urinary System
	0U Female Reproductive System
	0V Male Reproductive System
	0W Anatomical Regions, General
	0X Anatomical Regions, Upper Extremities
	0Y Anatomical Regions, Lower Extremities

Surgical procedures were identified using the ICD 9 and ICD 10 procedure codes listed, in the 30 days before the index date of the baseline initiation. Additionally, we also included patients discharged from a hospital surgical service in that same period.

Table S3. Morphine Milligram Equivalent (MME) conversion table

Opioid (strength in mg except where noted)	MME Conversion Factor*
Buprenorphine, transdermal patch (MCG/HR)	12.6
Buprenorphine, tablet or film	30
Buprenorphine, film (MCG)	0.03
Codeine	0.15
Fentanyl, buccal/SL tablet or lozenge/troche (MCG)	0.13
Fentanyl, film or oral spray (MCG)	0.18
Fentanyl, nasal spray (MCG)	0.16
Fentanyl, transdermal patch (MCG/HR)	7.2
Hydromorphone	4
Morphine	1
Oxycodone	1.5
Tapentadol	0.4
Tramadol	0.1

Source: CDC 2016.

*To be used in the formula: Strength per Unit X (Number of Units/ Days Supply) X MME conversion factor = MME/Day. Please see Documentation for additional information on using the formula with transdermal patches.

MCG: microgram; HR: hour

Table S4. International Classification of Diseases, 9th edition (ICD-9-CM) codes used for categories of indication of use

Indication	ICD9-CM codes	More prevalent codes in the study
Respiratory disorders	460* - 519*	460 Acute nasopharyngitis (common cold) 462 Acute pharyngitis 786 Symptoms involving the respiratory system and other thoracic symptoms 466 Acute bronchitis and bronchiolitis 487 Flu
Gastrointestinal disorders	520* - 579*	525 Other diseases and processes of teeth and supporting structures 536 Functional disorders of stomach 522 Diseases of the pulp and periapical tissues 455 Haemorrhoids 521 Diseases of hard tissues of teeth
Osteoarticular pain	696.0, 710*, 711*, 712. *, 713.*, 714*,715.*, 716.0*, 716.1*, 716.2*, 716.4*, 716.3*, 716.5*, 716.6*, 716.8*, 716.9*, 717*, 718*, 719*, 730.0*, 730.1*, 730.2*, 730.3*, 730.7*,730.8*,730.9*,731*,732*,733*, 734*,735*,736*,737*,738*,739*	719 Other and unspecified disorders of articulation 715 Osteoarthritis and related disorders 733 Other disorders of bone and cartilage 717 Internal disorder of knee
Back pain	720*, 721*, 722*, 723*, 724*	720 Ankylosing spondylitis and other inflammatory spondylitis 721 Spondylosis and related disorders 722 Intervertebral disc disorder 723 Other disorders of cervical region 724 Other and unspecified disorders of back
Reumathoid / arthritis	725, 726*, 727*,728*, 729*	726 Tendinitis of peripheral attachments and related syndromes 729 Other soft tissue disorders 728 Disorders of muscles, ligaments and fascia
Other musculoskeletal disorders	756*, 784.0, 784.1, 784.92, 786.5*, 788.0, 788.20, 788.29, 789.0*, 789.6*, 789.7, 800-897. *, 920. *, 921.0, 921.1, 922. *, 923. *, 924. *, 925-949. *, 953. *, 954.8, 954.9, 955-957. *, 958.9*, 959. *, 997.41, 997.62, V13.4, V13.5*, V43.6*	788 Symptoms affecting the urinary system 922 Contusion of trunk 784 Symptoms affecting head and neck 924 Contusion of lower limb and other sites and unspecified sites 789 Other symptoms involving the abdomen and pelvis
Miscellaneous	Infectious Diseases: 003.23, 003.24, 009*, 015*, 036.82, 040.0, 040.81, 053*, , 054.10, 054.11, 054.12, 054.13, 054.19, 056.71, 060*, 061*, 066.40, 066.49, 072.0, 072.3, 074.1, 074.20, 074.21, 074.23, 079*, 088.81, 095.5, 095.7, 099.3, 101, 112.84, 117.5, 122*, 135, 136.0, 136.1, 136.5, 137.3 321.2 Endocrine Disease: 244*, 245.0, 245.1, 249.60, 249.61, 249.70, 249.71, 250*, 251.5, 268.0, 268.1, 268.2, 272*, 277.1 Nutrition: 266.0, 266.2 Joint Disease: 135, 136.1, 274.0, 274.01, 274.00, 274.02, 274.03, 274.9, 275.01, 275.02, 275.03, 275.49, 277.2, 277.30, 277.31 Immune Disorders: 279.50, 279.51, 279.52, 279.53 Hematologic Disorders: 282.41, 282.42, 282.60, 282.61, 282.62, 282.63, 282.64, 282.68, 282.69, 286.0, 286.1, 289.1, 790*	053 Herpes zoster 009 Ill-defined intestinal infections 079Viral and Chlamydial infection in diseases classified elsewhere and of unspecified site 250 Diabetes mellitus 272 Lipid metabolism disorders 244 Acquired hypothyroidism 266 Deficiency of B complex components 274 Gout 279 Disorders involving the immune mechanism 790 Non-specific findings in the blood test

Neurologic Disorders (including headache): 321.4, 322.0, 322.1, 322.2, 322.9, 324.0, 324.1, 324.9, 325, 332.0*, 336.0, 339.00, 339.01, 339.02, 339.03, 339.04, 339.05, 339.09, 339.10, 339.11, 339.12, 339.20, 339.21, 339.22, 339.3, 339.41, 339.42, 339.43, 339.44, 339.81, 339.82, 339.83, 339.84, 339.85, 339.89, 340*, 341.0, 341.20, 341.21, 341.22, 346.00, 346.01, 346.02, 346.03, 346.1*, 346.2*, 346.3*, 346.4*, 346.5*, 346.6*, 346.7*, 346.8*, 346.9*, 349.0, 350.1, 350.2, 353*, 354*, 355*, 356.0, 356.2, 356.4, 356.8, 356.9, 357.0, 357.1, 357.2, 357.4, 357.5, 357.6, 357.7, 357.81, 357.82, 357.89, 357.9, 359.4, 359.5, 359.6, 359.7*, 359.8*, 359.9*, 430, 431*, 432*, 437.4, 437.6	346 Migraines 354 Mononeuritis of upper limb and mononeuritis multiplex 350 Disorders of trigeminal nerve 355 Mononeuritis of lower limb and unspecified site
Pain (cause unspecified): 338.0, 338.11, 338.12, 338.18, 338.19, 338.21, 338.22, 338.28, 338.29, 338.3, 338.4, 780*, 999*	338 Pain, not elsewhere classified 780 General symptoms
Eye Disorders: 360.03, 360.11, 360.12, 376.02, 376.03, 379.91	379 Other eye disorders
Ear Disorders: 380*, 382*, 383*, 388*	382 Otitis media, suppurative and unspecified 380 Disorders of external ear 383 Mastoiditis and related diseases
Cardiovascular Disorders: 390*, 391*, 393*, 401*, 415.1*, 420*, 422*, 429.0, 443.1, 443.8*, 443.9, 444.2*, 444.8*, 444.9, 445*, 446.0, 446.3, 446.4, 446.7, 447.6, 449*, 451*, 453.0, 453.1, 453.4*, 453.82, 453.83, 453.84, 453.89, 454.0, 454.1, 454.2, 454.8, 457.0, 457.1, 457.2, 459*	401 Essential hypertension 459 Other disorders of circulatory system
Genito urethral Disorders: 588.0, 590.00, 590.01, 590.10, 590.11, 590.2, 590.80, 590.81, 590.9, 591*, 592*, 595*, 596.6, 596.81, 599.0, 599.6, 599.60, 599.69, 601.2, 607.3, 608.2*, 611.0, 611.71, 614.1, 614.2, 614.4, 614.5, 616.5*, 614.7, 614.8, 614.9, 616.81, 616.89, 616.9, 617.* 620.5, 625*, 629.3*, 633.*, 639.0, 664.0*, 664.1*, 664.2*, 664.3*, 664.4*, 664.6*, 664.8*, 664.9*, 665.0*, 665.1*, 665.3*, 665.4*, 665.5*, 665.8*, 665.9*, 673.*, 674.1*, 674.2*, 674.3*	595 Cystitis 599 Other disorders of urethra and urinary tract 592 Calculus of kidney and ureter
Skin Disorders: 682*, 683*, 686.01, 692*, 694.4, 695.2, 695.81, 705.83, 707*, 782*	682 Other cellulitis and abscess 782 Symptoms of affecting the skin and other integumentary tissue 707 Chronic ulcer of skin
Mental Disorders: 300*, 307.80, 307.81, 307.89, 311*	300 Anxiety, dissociative and somatoform disorders 307 Special symptoms or syndromes, not elsewhere classified 311 Depressive disorder, not elsewhere classified
Other: V01-V87, Except: V13.4, V13.5*, V43.6*	V66 Convalescence and palliative care V54 Other orthopaedic aftercare

Adapted from: Zhu W, Chernew ME, Sherry TB, Maestas N. Initial Opioid Prescriptions among U.S. Commercially Insured Patients, 2012-2017. *N Engl J Med*. 2019 Mar 14;380(11):1043-1052. doi: 10.1056/NEJMsa1807069. PMID: 30865798; PMCID: PMC6487883.

Figure S5. Kaplan Meier survival curves, per type of opioid and per specific drug.

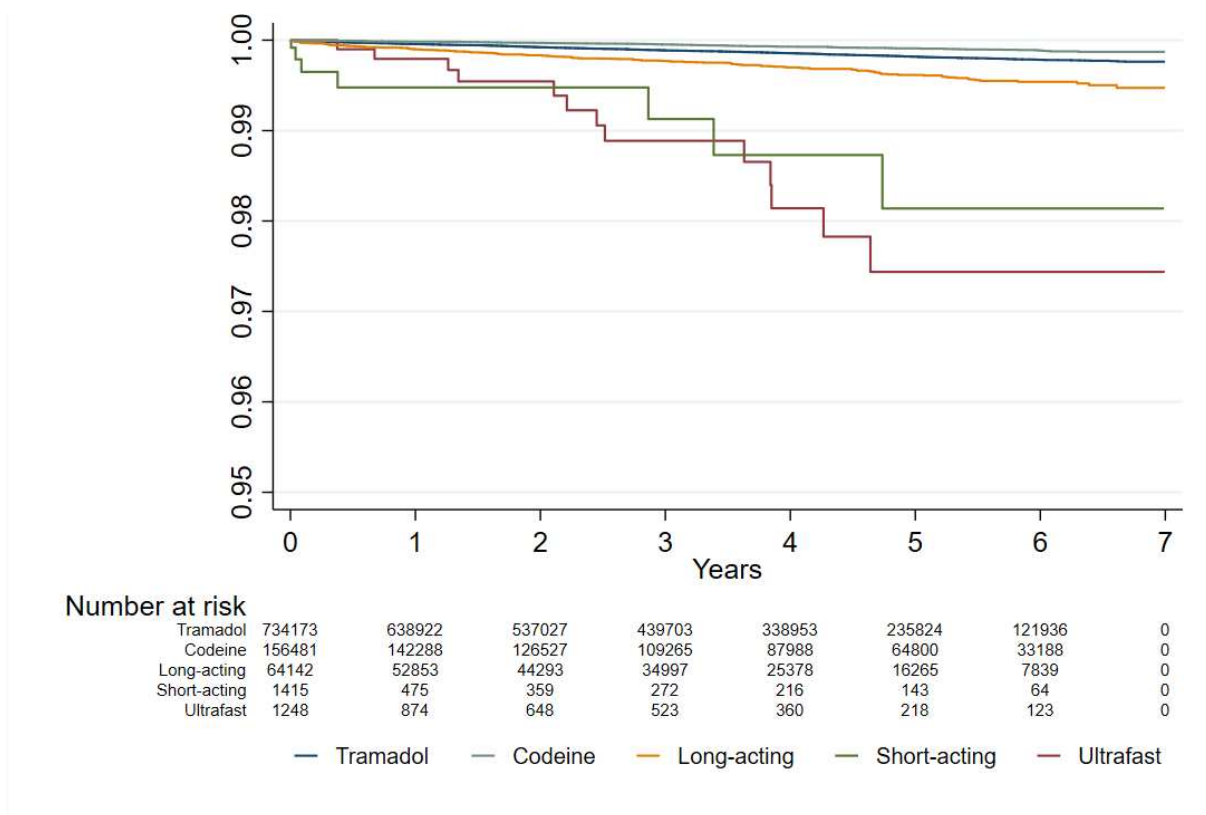


Figure S5. Kaplan Meier survival curves, per type of opioid and per specific drug.

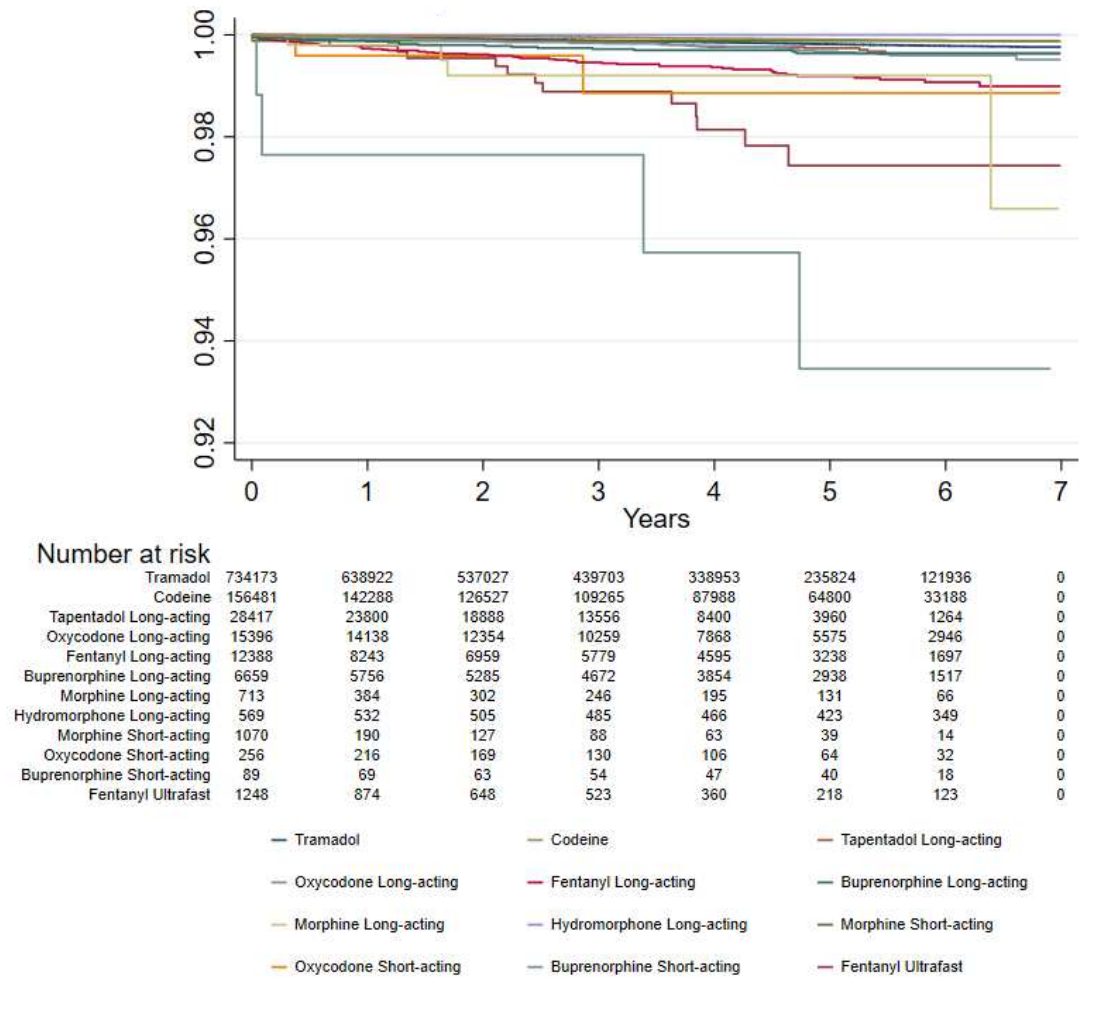


Table S6. Results of the shared frailty Cox model, opioids per type.

	Hazard ratio	Lower interval	Upper interval	p value
Sex				
Men	2.38	2.11	2.68	<0.001
Age range				
18-44	1.00			
45-64	0.45	0.39	0.52	<0.001
65-74	0.42	0.34	0.52	<0.001
>=75	0.69	0.56	0.85	<0.001
Income level (yearly, euros)				
<18.000	1.00			
18.000-100.000	0.58	0.48	0.71	<0.001
>100.000	1.40	0.45	4.34	0.57
No resources	2.13	1.82	2.49	<0.001
Unknown	2.82	1.40	5.69	0.00
Nationality				
Spain	1.00			
European	1.24	1.01	1.52	0.04
Non-European	0.50	0.37	0.66	<0.001
Unknown	1.25	0.84	1.86	0.26
Clinical conditions				
Surgical procedure (in the previous 30 days before initiation)	1.19	0.89	1.58	0.25
Ischemic cardiomyopathy	1.25	1.01	1.55	0.05
Congestive Obstructive Pulmonary Disease	1.54	1.28	1.84	<0.001
Dementia	0.98	0.72	1.33	0.89
Depression	1.41	1.23	1.61	<0.001
Diabetes	1.01	0.86	1.18	0.94
Heart Failure	1.64	1.27	2.12	<0.001
Hypertension	0.79	0.69	0.91	0.00
Renal disease	1.40	1.13	1.74	0.00
Liver disease	1.52	1.28	1.80	<0.001
Lifestyle				
Alcohol	2.89	2.40	3.47	<0.001
Tobacco	1.26	1.09	1.46	0.00
Action				
Tramadol	1.00			
Ultrafast	7.22	4.13	12.62	<0.001
Short acting	4.80	2.26	10.22	<0.001
Long acting	1.52	1.24	1.87	<0.001
Codeine	0.62	0.49	0.78	<0.001

Indication of use				
Back pain	1.00			
Gastrointestinal pain	1.11	0.85	1.45	0.44
Osteoarticular	0.92	0.77	1.11	0.39
Respiratory	1.01	0.77	1.31	0.97
Rheumatoid pain	0.95	0.74	1.22	0.69
Other musculoskeletal	1.49	1.25	1.78	<0.001
Miscellaneous	1.42	1.21	1.66	<0.001
Duration (days)				
1 to 3	1.00			
4 to 7	1.34	1.00	1.79	0.05
8 to 14	1.40	1.04	1.89	0.03
15 to 30	1.67	1.23	2.28	0.00
>=31	1.80	1.30	2.48	<0.001
Daily morphine milligram equivalent, range				
<50	1.00			
50-89	1.17	0.89	1.55	0.26
90-119	1.18	0.66	2.13	0.57
>=120	1.59	1.15	2.19	0.01
Overlapping medication				
Benzodiazepines	2.09	1.85	2.36	<0.001
Gabapentinoids	1.74	1.46	2.08	<0.001
Antipsychotics	2.67	2.21	3.23	<0.001
Random effect				
theta	0.10			0.04

Table S7. Results of the shared frailty Cox model, opioids per specific drug.

	Hazard ratio	Lower interval	Upper interval	p value
Sex				
Men	2.38	2.11	2.68	<0.001
Age range				
18-44	1.00			
45-64	0.45	0.39	0.52	<0.001
65-74	0.42	0.34	0.52	<0.001
>=75	0.69	0.56	0.84	<0.001
Income level (yearly, euros)				
<18.000	1.00			
18.000-100.000	0.59	0.48	0.71	<0.001
>100.000	1.40	0.45	4.34	0.57
No resources	2.12	1.81	2.49	<0.001
Unknown	2.78	1.38	5.61	0.00
Nationality				
Spain	1.00			
European	1.24	1.01	1.53	0.04
Non-European	0.49	0.37	0.66	<0.001
Unknown	1.26	0.85	1.87	0.25
Clinical conditions				
Surgical procedure (in the previous 30 days before initiation)	1.14	0.85	1.53	0.38
Ischemic cardiomyopathy	1.25	1.01	1.56	0.04
Congestive Obstructive Pulmonary Disease	1.53	1.28	1.83	<0.001
Dementia	0.97	0.72	1.32	0.85
Depression	1.41	1.23	1.62	<0.001
Diabetes	1.00	0.86	1.18	0.96
Heart Failure	1.62	1.25	2.10	<0.001
Hypertension	0.79	0.69	0.91	0.00
Renal disease	1.38	1.12	1.72	0.00
Liver disease	1.51	1.28	1.79	<0.001
Lifestyle				
Alcohol	2.88	2.39	3.46	<0.001
Tobacco	1.26	1.09	1.46	0.00
Action				
Tramadol	1.00			
Fentanyl ultrafast	7.21	4.11	12.63	<0.001
Morphine short-acting	1.21	0.17	8.67	0.85
Oxycodone short-acting	4.49	1.11	18.23	0.04
Buprenorphine short-acting	23.65	8.83	63.33	<0.001
Fentanyl long-acting	2.66	1.96	3.61	<0.001

Hydromorphone long-acting	0.00			
Morphine long-acting	3.40	1.27	9.13	0.02
Tapentadol long-acting	1.08	0.78	1.48	0.66
Oxycodone long-acting	1.47	1.06	2.04	0.02
Buprenorphine long-acting	0.95	0.53	1.69	0.85
Codeine	0.62	0.49	0.78	<0.001
Indication of use				
Back pain	1.00			
Gastrointestinal pain	1.09	0.84	1.43	0.52
Osteoarticular	0.92	0.76	1.11	0.38
Respiratory	1.00	0.76	1.30	0.97
Rheumatoid pain	0.95	0.74	1.22	0.69
Other musculoskeletal	1.49	1.25	1.77	<0.001
Miscellaneous	1.40	1.20	1.64	<0.001
Duration (days)				
1 to 3	1.00			
4 to 7	1.36	1.01	1.82	0.04
8 to 14	1.41	1.04	1.91	0.03
15 to 30	1.72	1.26	2.36	<0.001
>=31	1.83	1.32	2.54	<0.001
Daily morphine milligram equivalent, range				
<50	1.00			
50-89	1.10	0.83	1.46	0.51
90-119	1.16	0.64	2.08	0.63
>=120	1.85	1.27	2.70	0.00
Overlapping medication				
Benzodiazepines	2.08	1.84	2.35	<0.001
Gabapentinoids	1.74	1.46	2.08	<0.001
Antipsychotics	2.65	2.20	3.21	<0.001
Random effect				
Theta	0.10			0.04

Table S8. Results of the Cox model including competing risk of death, opioids per type.

	Hazard ratio	Lower interval	Upper interval	p value
Sex				
Men	2.25	1.97	2.57	<0.001
Age range				
18-44	1.00			
45-64	0.44	0.38	0.51	<0.001
65-74	0.34	0.27	0.43	<0.001
>=75	0.42	0.33	0.53	<0.001
Income level (yearly, euros)				
<18.000	1.00			
18.000-100.000	0.59	0.47	0.73	<0.001
>100.000	0.61	0.09	4.32	0.619
No resources	2.08	1.74	2.47	<0.001
Unknown	1.86	0.83	4.15	0.129
Nationality				
Spain	1.00			
European	1.34	1.08	1.66	0.007
Non-European	0.51	0.37	0.70	<0.001
Unknown	1.55	1.01	2.40	0.047
Clinical conditions				
Surgical procedure (in the previous 30 days before initiation)	0.98	0.68	1.42	0.926
Ischemic cardiomyopathy	1.11	0.83	1.48	0.495
Congestive Obstructive Pulmonary Disease	1.34	1.06	1.68	0.013
Dementia	0.56	0.35	0.88	0.012
Depression	1.44	1.24	1.69	<0.001
Diabetes	0.85	0.70	1.03	0.097
Heart Failure	0.98	0.66	1.45	0.92
Hypertension	0.73	0.63	0.85	<0.001
Renal	1.18	0.89	1.56	0.258
Liver	1.52	1.25	1.84	<0.001
Lifestyle				
Alcohol	2.85	2.28	3.55	<0.001
Tobacco	1.29	1.09	1.52	0.003
Action				

Tramadol	1.00			
Ultrafast	4.52	2.16	9.47	<0.001
Short acting	3.29	1.39	7.79	0.007
Long acting	1.39	1.09	1.77	0.008
Codeine	0.67	0.51	0.88	0.003
Indication of use				
Back pain	1.00			
Gastrointestinal pain	1.11	0.84	1.49	0.46
Osteoarticular	0.86	0.69	1.07	0.17
Respiratory	0.92	0.68	1.26	0.611
Rheumatoid pain	0.91	0.68	1.20	0.498
Other musculoskeletal	1.51	1.25	1.83	<0.001
Miscellaneous	1.39	1.16	1.66	<0.001
Duration (days)				
1 to 3	1.00			
4 to 7	1.27	0.93	1.73	0.139
8 to 14	1.30	0.94	1.80	0.114
15 to 30	1.53	1.08	2.16	0.016
>=31	1.76	1.24	2.50	0.002
Daily morphine milligram equivalent, range				
<50	1.00			
50-89	1.02	0.74	1.41	0.889
90-119	1.29	0.69	2.42	0.423
>=120	1.67	1.14	2.44	0.008
Overlapping medication	1.00			
Benzodiazepines	2.18	1.90	2.52	<0.001
Gabapentinoids	1.91	1.57	2.33	<0.001
Antipsychotics	2.77	2.24	3.43	<0.001

Table S9. Results of the Cox model including competing risk of death, opioids per specific drug.

Sex	Hazard ratio	Lower interval	Upper interval	P value
Men	2.25	1.97	2.56	<0.001
Age range				
18-44	1.00			
45-64	0.44	0.38	0.51	<0.001
65-74	0.34	0.27	0.43	<0.001
>=75	0.42	0.33	0.53	<0.001
Income level (yearly, euros)				
<18.000	1.00			
18.000-100.000	0.59	0.47	0.73	<0.001
>100.000	0.62	0.09	4.38	0.628
No resources	2.08	1.74	2.47	<0.001
Unknown	1.85	0.83	4.14	0.135
Nationality				
Spain	1.00			
European	1.34	1.08	1.66	0.007
Non-European	0.51	0.37	0.70	<0.001
Unknown	1.57	1.02	2.43	0.041
Clinical conditions				
Surgical procedure (in the previous 30 days before initiation)	0.97	0.67	1.41	0.873
Ischemic cardiomyopathy	1.11	0.83	1.48	0.482
Congestive Obstructive Pulmonary Disease	1.33	1.06	1.68	0.014
Dementia	0.57	0.36	0.90	0.017
Depression	1.45	1.24	1.69	<0.001
Diabetes	0.85	0.69	1.03	0.094
Heart Failure	0.99	0.67	1.46	0.946
Hypertension	0.73	0.62	0.85	<0.001
Renal disease	1.18	0.89	1.57	0.249
Liver disease	1.51	1.25	1.84	<0.001
Lifestyle				
Alcohol	2.84	2.28	3.54	<0.001
Tobacco	1.29	1.09	1.52	0.003
Action				

Tramadol	1.00			
Fentanyl ultrafast	4.35	2.05	9.23	<0.001
Morphine short-acting	0.73	0.10	5.39	0.759
Oxycodone short-acting	3.03	0.41	22.42	0.279
Buprenorphine short-acting	25.15	9.30	68.00	<0.001
Fentanyl long-acting	1.68	1.11	2.55	0.015
Hydromorphone long-acting	0.00	0.00	0.00	<0.001
Morphine long-acting	2.26	0.72	7.08	0.161
Tapentadol long-acting	1.14	0.80	1.63	0.46
Oxycodone long-acting	1.57	1.10	2.25	0.013
Buprenorphine long-acting	0.89	0.45	1.78	0.744
Codeine	0.67	0.51	0.88	0.004
Indication of use				
Back pain	1.00			
Gastrointestinal pain	1.11	0.83	1.48	0.489
Osteoarticular	0.86	0.69	1.07	0.165
Respiratory	0.92	0.68	1.26	0.614
Rheumatoid pain	0.90	0.68	1.19	0.465
Other musculoskeletal	1.50	1.24	1.82	<0.001
Miscellaneous	1.38	1.16	1.65	<0.001
Duration (days)				
1 to 3	1.00			
4 to 7	1.30	0.94	1.79	0.115
8 to 14	1.33	0.95	1.87	0.093
15 to 30	1.57	1.10	2.25	0.013
>=31	1.82	1.26	2.61	0.001
Daily morphine milligram equivalent, range				
<50	1.00			
50-89	1.02	0.74	1.42	0.895
90-119	1.33	0.71	2.49	0.378
>=120	1.95	1.24	3.07	0.004
Overlapping medication				
Benzodiazepines	2.18	1.89	2.51	<0.001
Gabapentinoids	1.92	1.58	2.33	<0.001
Antipsychotics	2.76	2.23	3.42	<0.001

Table S10. Results of the shared frailty Cox model excluding groups of ultrafast and short-acting initial prescription, opioids per type.

	Hazard ratio	Lower interval	Upper interval	P value
Sex				
Men	2.39	2.12	2.70	<0.001
Age range				
18-44	1.00			
45-64	0.45	0.39	0.52	<0.001
65-74	0.41	0.33	0.50	<0.001
>=75	0.70	0.57	0.85	<0.001
Nationality				
Spain	1.00			
European	1.25	1.02	1.54	0.03
Non-European	0.47	0.35	0.63	<0.001
Unknown	1.30	0.87	1.92	0.20
Income level (yearly, euros)				
<18.000	1.00			
18.000-100.000	0.59	0.49	0.72	<0.001
>100.000	1.43	0.46	4.43	0.54
No resources	2.11	1.80	2.48	<0.001
Unknown	2.93	1.45	5.92	0.00
Lifestyle				
Alcohol	2.90	2.40	3.49	<0.001
Tobacco	1.25	1.08	1.45	0.00
Clinical conditions				
Surgical procedure (in the previous 30 days before initiation)	1.19	0.89	1.60	0.24
Ischemic cardiomyopathy	1.25	1.00	1.56	0.05
Congestive Obstructive Pulmonary Disease	1.55	1.29	1.86	<0.001
Dementia	1.04	0.76	1.40	0.83
Depression	1.40	1.22	1.61	<0.001
Diabetes	1.01	0.86	1.19	0.88
Heart Failure	1.70	1.32	2.21	<0.001
Hypertension	0.78	0.68	0.90	<0.001
Renal disease	1.41	1.14	1.75	0.00
Liver disease	1.53	1.29	1.82	<0.001
Action				
Tramadol	1.00			
Long acting	1.48	1.20	1.82	<0.001
Codeine	0.61	0.48	0.77	<0.001
Duration (days)				
1 to 3	1.00			
4 to 7	1.34	1.00	1.81	0.05

8 to 14	1.41	1.04	1.91	0.03
15 to 30	1.67	1.21	2.29	0.00
>=31	1.84	1.32	2.55	<0.001
Daily morphine milligram equivalent, range				
<50	1.00			
50-89	1.19	0.89	1.58	0.24
90-119	1.18	0.64	2.17	0.61
>=120	1.72	1.24	2.38	0.00
Indication of use				
Back pain	1.00			
Gastrointestinal pain	1.13	0.87	1.48	0.36
Osteoarticular	0.92	0.76	1.10	0.36
Respiratory	1.02	0.78	1.34	0.88
Rheumatoid pain	0.95	0.74	1.22	0.68
Other musculoskeletal	1.49	1.24	1.77	<0.001
Miscellaneous	1.44	1.23	1.68	<0.001
Overlapping medication				
Benzodiazepines	2.08	1.84	2.34	<0.001
Gabapentinoids	1.73	1.44	2.07	<0.001
Antipsychotics	2.70	2.23	3.27	<0.001
Random effect				
theta	0.10			

Table S11. Results of the shared frailty Cox model excluding groups of ultrafast and short-acting initial prescription, opioids per specific drug.

	Hazard ratio	Lower interval	Upper interval	P value
Sex				
Men	2.38	2.11	2.69	<0.001
Age range				
18-44	1.00			
45-64	0.45	0.39	0.52	<0.001
65-74	0.41	0.33	0.50	<0.001
>=75	0.69	0.56	0.85	<0.001
Nationality				
Spain	1.00			
European	1.25	1.02	1.54	0.03
Non-European	0.47	0.35	0.63	<0.001
Unknown	1.29	0.87	1.90	0.21
Income level (yearly, euros)				
<18.000	1.00			
18.000-100.000	0.59	0.49	0.72	<0.001
>100.000	1.41	0.45	4.39	0.55
No resources	2.11	1.80	2.48	<0.001
Unknown	2.89	1.43	5.83	0.00
Lifestyle				
Alcohol	2.88	2.39	3.47	<0.001
Tobacco	1.25	1.07	1.44	0.00
Clinical conditions				
Surgical procedure (in the previous 30 days before initiation)	1.14	0.85	1.53	0.39
Ischemic cardiomyopathy	1.25	1.00	1.56	0.05
Congestive Obstructive Pulmonary Disease	1.53	1.28	1.84	<0.001
Dementia	1.01	0.75	1.37	0.94
Depression	1.41	1.23	1.61	<0.001
Diabetes	1.01	0.86	1.18	0.93
Heart Failure	1.66	1.28	2.15	<0.001
Hypertension	0.79	0.68	0.91	<0.001
Renal disease	1.39	1.11	1.72	0.00
Liver disease	1.52	1.29	1.81	<0.001
Action				

Tramadol	1.00			
Fentanyl long-acting	2.56	1.88	3.48	<0.001
Hydromorphone long-acting	0.00			
Morphine long-acting	3.32	1.24	8.93	0.02
Tapentadol long-acting	1.05	0.76	1.45	0.76
Oxycodone long-acting	1.46	1.05	2.03	0.03
Buprenorphine long-acting	0.85	0.47	1.52	0.58
Codeine	0.62	0.49	0.78	<0.001
Duration (days)				
1 to 3	1.00			
4 to 7	1.37	1.01	1.85	0.04
8 to 14	1.43	1.05	1.94	0.03
15 to 30	1.73	1.25	2.38	<0.001
>=31	1.87	1.34	2.61	<0.001
Daily morphine milligram equivalent, range				
<50	1.00			
50-89	1.11	0.83	1.48	0.49
90-119	1.14	0.62	2.11	0.68
>=120	2.08	1.42	3.03	<0.001
Indication of use				
Back pain	1.00			
Gastrointestinal pain	1.11	0.85	1.46	0.43
Osteoarticular	0.92	0.76	1.10	0.36
Respiratory	1.00	0.77	1.31	0.98
Rheumatoid pain	0.95	0.74	1.23	0.70
Other musculoskeletal	1.48	1.24	1.77	<0.001
Miscellaneous	1.42	1.21	1.66	<0.001
Overlapping medication				
Benzodiazepines	2.07	1.83	2.34	<0.001
Gabapentinoids	1.73	1.45	2.08	<0.001
Antipsychotics	2.68	2.21	3.24	<0.001
Random effect				
theta	0.10			