

## Supplementary Material

Long vs short-term opioid therapy for fibromyalgia syndrome and risk of depression, sleep disorders and suicidal ideation: a population-based, propensity-weighted cohort study.

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**Table S1. International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) codes for comorbidities, cancer exclusion criterion, lifestyle variables and outcomes.****Comorbidities**

Hypertension	ICD9 diagnosis 401.xx-405.xx, 437.2 ICD10 diagnosis I10.x-I13.x, I15.x, I67.4
Heart Failure	ICD9 diagnosis 428.xx, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.03, 404.13, 404.91, 404.93, 425.4x ICD10 diagnosis I50.x, I11.0, I13.0, I13.2, I42.0
Ischemic cardiomyopathy	ICD9 diagnosis 410.xx-414.xx ICD10 diagnosis I20.x-I25.x
COPD	ICD9 diagnosis 491.xx, 492.xx, 496.xx, 493.20, 493.21, 493.22 ICD10 diagnosis J41.x- J44.x
Diabetes	ICD9 diagnosis 249.xx, 250.xx, 648.0 ICD10 diagnosis E08.x, E09.x, E10.x, E11.x, E13.x
Renal disease	ICD9 diagnosis 403.x, 404.x, 580.x-589.x, 590.1, 753.x, 792.5, V42.0, V45.1, V56.x ICD10 diagnosis I12.x, I13.x, N00.x-N05.x, N07.x, N11.x, N14.x, N17.x-N19.x, Q61.x, Z49.x, Z94.0, Z91.15, Z99.2
Liver disease	ICD9 diagnosis 070.0, 070.2x, 070.4x, 070.6x, 070.71, 570.xx-573.xx, 782.4x, 789.1x, 789.5x, 790.4x, 790.5x, 794.8x ICD10 diagnosis B19.11, B15.0x, B16.0, B16.2, B19.0, I85.x, K70.x-K77.x, R17.x, R18.x, R74.x, R94.5, Z94.4
Dementia	ICD9 diagnosis 290.xx, 294.xx, 330.xx, 331.xx ICD10 diagnosis F00.x- F03.x, G30.x, G31.x
Depression	ICD9 diagnosis 296.2x, 296.3x, 298.0, 300.4x, 301.12, 311.xx ICD10 diagnosis F32.x-F33.x; F34.1
Drug use	ICD9 diagnosis 292.xx, 304.xx, 305.2x-305.9x ICD10 diagnosis F11.x-F16.x; F18.x-F19.x

Personality disorders	ICD9 diagnosis 301.xx
	ICD10 diagnosis F60.x 290.x-299.x ICD10 diagnosis F20.x-F29.x
Other psychiatric disorders	ICD9 diagnosis 296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x, 296.99 ICD10 diagnosis F31.x
	ICD9 diagnosis 302.xx ICD10 diagnosis F64.x;F65.x;F66.x  ICD9 diagnosis 308.xx acute reaction to stress (exclude 308.0x, Anxiety as acute reaction to exceptional stress); 309.x; 312.x ICD10 diagnosis F43.x; F91.x  314.xx ICD10 diagnosis F90.x
Anxiety	ICD9 diagnosis 300.x ICD10 diagnosis F40.x-F48.x
<b>Lifestyle variables</b>	
Alcohol use	ICD9 diagnosis 291.xx, 303.xx, 305.0x, 571.0x, 571.1x, 571.2x, 571.3x, 357.5x, 425.5x, E860.0x ICD10 diagnosis F10.x; K70.x; G62.1; I42.6
Tobacco use	ICD9 diagnosis 305.1,989.84,V15.82 ICD10 diagnosis F17.x,T65.2
<b>Exclusion criterion</b>	
Cancer	ICD9 140.xx-208.xx ICD10 C00.x-C96.x
<b>Outcomes</b>	
Suicidal ideation	ICD9 diagnosis E95.x,V62.84, 300.9 ICD10 diagnosis

	<p>T36.92X , T37.92X , T39.92X , T41.42X , T42.72X , T43.92X , T45.92X, T47.92X , T49.92X , T51.92X , T52.92X , T53.92X , T54.92X , T56.92X , T57.92X , T59.92X , T60.92X , T61.92X , T62.92X , T63.92X , T65.92X , X71.x-X83.x , T58.02X , T58.03X , T58.04X , T58.05X , T58.06X , T58.07X , T58.08X, T58.09X , T58.10X , T58.11X , T58.12X, T61.02X , T61.03X , T61.04X , T61.05X , T61.06X , T61.07X , T61.08X), T61.09X , T61.10X , T61.11X , T61.12X, T64.02X , T64.03X , T64.04X , T64.05X , T64.06X , T64.07X , T64.08X, T64.09X , T64.10X , T64.11X , T64.12X, R45.851 T14.91X, Z91.5, T14.91,</p> <p>T36–T65 with the 6th character of 2 (except for T36.9, T37.9, T39.9, T41.4, T42.7, T43.9, T45.9, T47.9, T49.9, T51.9, T52.9, T53.9, T54.9, T56.9, T57.9, T58.0, T58.1, T58.9, T59.9, T60.9, T61.0, T61.1, T61.9, T62.9, T63.9, T64.0, T64.8, and T65.9, which are included if the 5th character is 2)</p>
Sleep disorders	<p>ICD9 diagnosis 307.4x, 327.xx, 347.xx , 780.5x</p> <p>ICD10 diagnosis G47.x; F51.x; Z72.82x</p>
Depression	<p>ICD9 diagnosis 296.2x. 296.3x, 298.0, 300.4x, 301.12, 311.xx</p> <p>ICD10 diagnosis F32.x-F33.x; F34.1</p>

**Table S2 Anatomical Therapeutic Chemical classification -ATC- codes of drugs included in the study.**

**ATC codes used for medication**

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

**Table S3. Morphine Milligram Equivalents conversion table.**

<b>Opioid (strength in mg except where noted)</b>	<b>MME Conversion Factor*</b>
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.

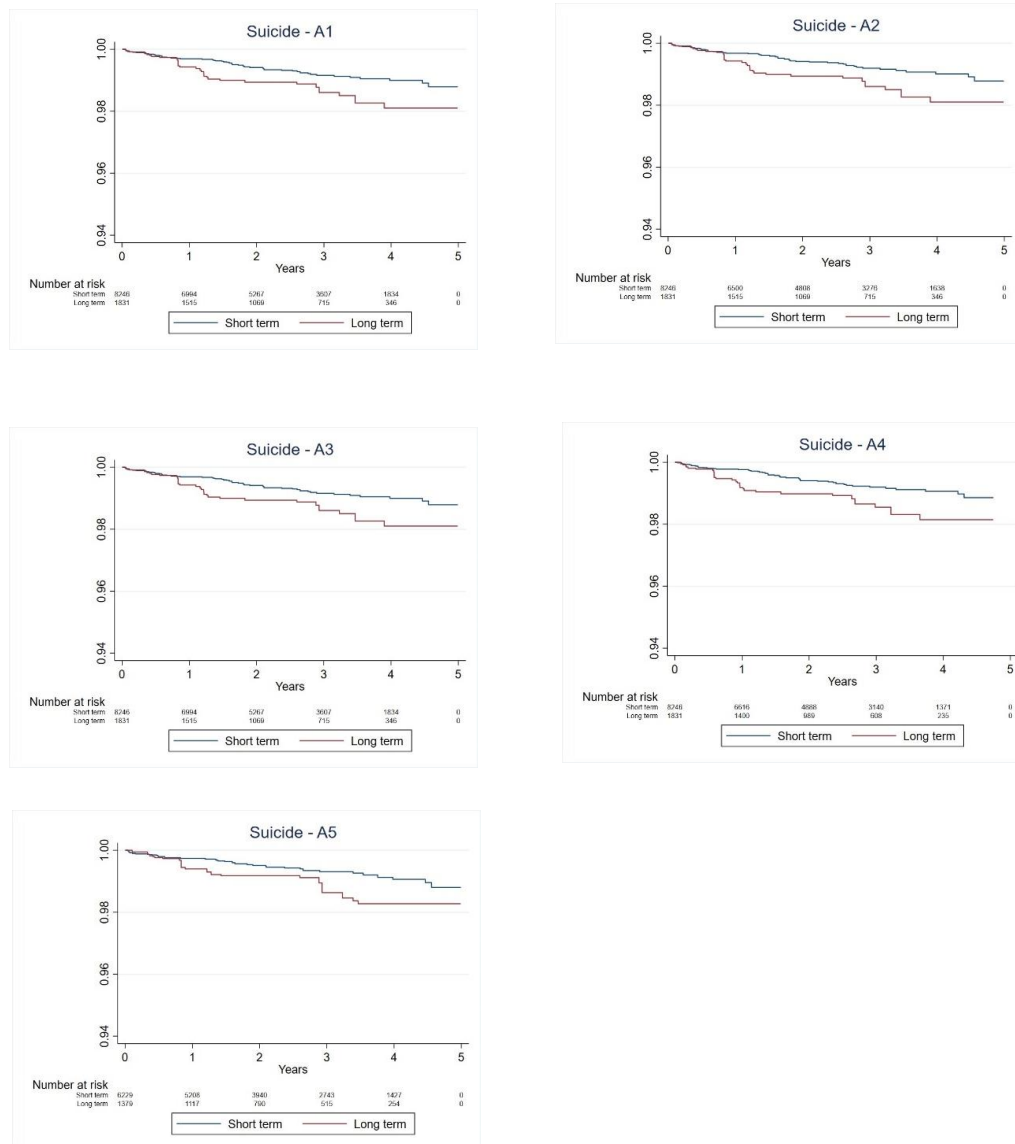
MCG: microgram; HR: hour

**Table S4. Standardized Mean Differences (SMD) before and after IPTW for analyses using prescription and dispensation data for all outcomes**

	Analyses with prescription data						Analyses with dispensation data					
	Suicidal ideation		Sleep disorders		Depression		Suicidal ideation		Sleep disorders		Depression	
	SMD before	SMD after	SMD before	SMD after	SMD before	SMD after	SMD before	SMD after	SMD before	SMD after	SMD before	SMD after
<i>Age range, years</i>												
18-44	-0.195	-0.096	-0.200	-0.111	-0.224	-0.111	-0.265	-0.111	-0.277	-0.133	-0.279	-0.119
45-64	0.230	0.066	0.222	0.073	0.235	0.061	0.191	0.039	0.196	0.050	0.166	0.017
65-74	-0.015	0.017	-0.018	0.022	-0.008	0.028	0.057	0.041	0.049	0.049	0.066	0.058
>=75	-0.094	0.000	-0.059	0.009	-0.057	0.021	-0.041	0.027	-0.004	0.039	0.017	0.054
<i>Sex</i>												
Men	-0.507	-0.223	-0.528	-0.231	-0.519	-0.217	-0.510	-0.232	-0.547	-0.254	-0.501	-0.221
<i>Income level, euros/year</i>												
<18.000	-0.053	-0.018	-0.027	-0.023	-0.044	-0.022	-0.097	-0.023	-0.046	-0.026	-0.089	-0.027
18.000-100.000	0.000	0.002	0.002	0.004	-0.002	0.002	-0.020	0.003	-0.016	0.003	-0.019	0.000
>100.000	-0.007	-0.016	-0.005	-0.018	-0.004	-0.023	-0.034	-0.044	-0.017	-0.034		
No resources	0.080	0.028	0.045	0.033	0.068	0.037	0.167	0.036	0.095	0.042	0.155	0.044
Unknown	-0.011	-0.009	-0.023	-0.011	0.009	-0.006	-0.026	-0.017	-0.038	-0.023	-0.009	-0.019
<i>Comorbidities</i>												
Ischemic cardiomyopathy	-0.071	-0.033	-0.066	-0.022	-0.094	-0.034	-0.026	-0.013	-0.022	-0.011	-0.045	0.001
COPD	0.044	0.029	0.063	0.036	0.033	0.027	0.073	0.030	0.062	0.028	0.026	0.028
Dementia	0.062	0.024	0.030	0.027	0.073	0.034	0.093	0.040	0.066	0.041	0.105	0.037
Depression	0.409	0.111	0.403	0.112	NA	NA	0.460	0.113	0.444	0.116	NA	NA
Diabetes	-0.027	-0.009	-0.021	-0.003	-0.068	-0.012	0.031	0.005	0.035	0.014	-0.009	0.004
Heart failure	-0.005	0.002	0.010	0.001	-0.023	-0.001	0.014	0.007	0.015	0.000	-0.008	0.005
Hypertension	0.070	0.038	0.103	0.049	0.073	0.059	0.115	0.047	0.145	0.064	0.113	0.064
Renal disease	0.001	0.002	0.012	0.003	-0.006	0.009	0.030	0.015	0.044	0.022	0.014	0.034
Liver disease	0.086	0.011	0.054	0.002	0.051	0.020	0.108	0.012	0.056	-0.004	0.084	0.014
Anxiety	0.352	0.111	0.363	0.119	0.296	0.096	0.337	0.115	0.351	0.129	0.246	0.096
Drug abuse	-0.018	-0.015	-0.038	-0.019	-0.089	-0.061	0.010	-0.012	-0.015	-0.033	-0.068	-0.044
Personality disorders	0.043	-0.001	0.042	-0.006	0.006	-0.002	0.077	0.007	0.067	0.006	0.024	0.022
Psychotic disorders	0.151	0.045	0.139	0.046	0.076	0.027	0.179	0.044	0.146	0.034	0.117	0.043
Other psychiatric disorders	0.157	0.050	0.176	0.049	0.157	0.048	0.188	0.052	0.204	0.060	0.198	0.054
Sleep Disorder	0.226	0.061	NA	NA	0.205	0.062	0.236	0.060	NA	NA	0.199	0.058
Previous suicidal ideation	NA	NA	0.006	0.017	0.031	0.005	NA	NA	-0.001	0.004	0.012	-0.006
<i>Lifestyle</i>												
Alcohol use	-0.041	-0.022	-0.091	-0.046	-0.063	-0.032	-0.027	-0.010	-0.078	-0.043	-0.042	-0.004
Tobacco use	0.055	0.011	0.048	0.006	0.052	0.008	0.063	0.001	0.046	-0.005	0.042	0.006
<i>Choice of opioid</i>												
Tramadol	-0.128	-0.003	-0.104	0.015	-0.081	0.013	-0.222	-0.036	-0.185	-0.027	-0.164	-0.021
Fentanyl Long-acting	0.154	0.051	0.156	0.056	0.159	0.071	0.170	0.036	0.169	0.043	0.175	0.055
Tapentadol Long-acting	0.190	0.059	0.179	0.056	0.178	0.074	0.413	0.210	0.398	0.217	0.383	0.223
Oxycodone Long-acting	0.138	0.036	0.125	0.036	0.126	0.042	0.088	0.011	0.077	0.012	0.055	0.010
Buprenorphine Long-acting	0.046	0.015	0.061	0.022	0.024	0.023	0.073	0.019	0.050	0.009	0.059	0.028
Codeine	-0.240	-0.124	-0.260	-0.153	-0.263	-0.174	-0.239	-0.117	-0.252	-0.132	-0.248	-0.150
<i>Daily Morphine Milligram Equivalent</i>												
Daily MME	0.167	0.051	0.172	0.051	0.134	0.054	0.158	0.046	0.155	0.049	0.152	0.057
<i>Overlapping medication</i>												
Benzodiazepines	0.355	0.102	0.373	0.099	0.306	0.089	0.410	0.102	0.407	0.097	0.343	0.088
Gabapentinoids	0.313	0.082	0.349	0.093	0.331	0.107	0.344	0.070	0.384	0.079	0.359	0.081
Antipsychotics	0.081	0.039	0.068	0.037	0.079	0.039	0.134	0.036	0.107	0.034	0.113	0.040

*IPTW: inverse probability of treatment weighting; COPD: congestive obstructive pulmonary disease.*

**Figure S5. Kaplan Meier curves for suicidal ideation, for each analysis for short-term and long-term users.**



A1: Main analysis

A2: Analysis censoring short-term users if they initiate long-term opioids

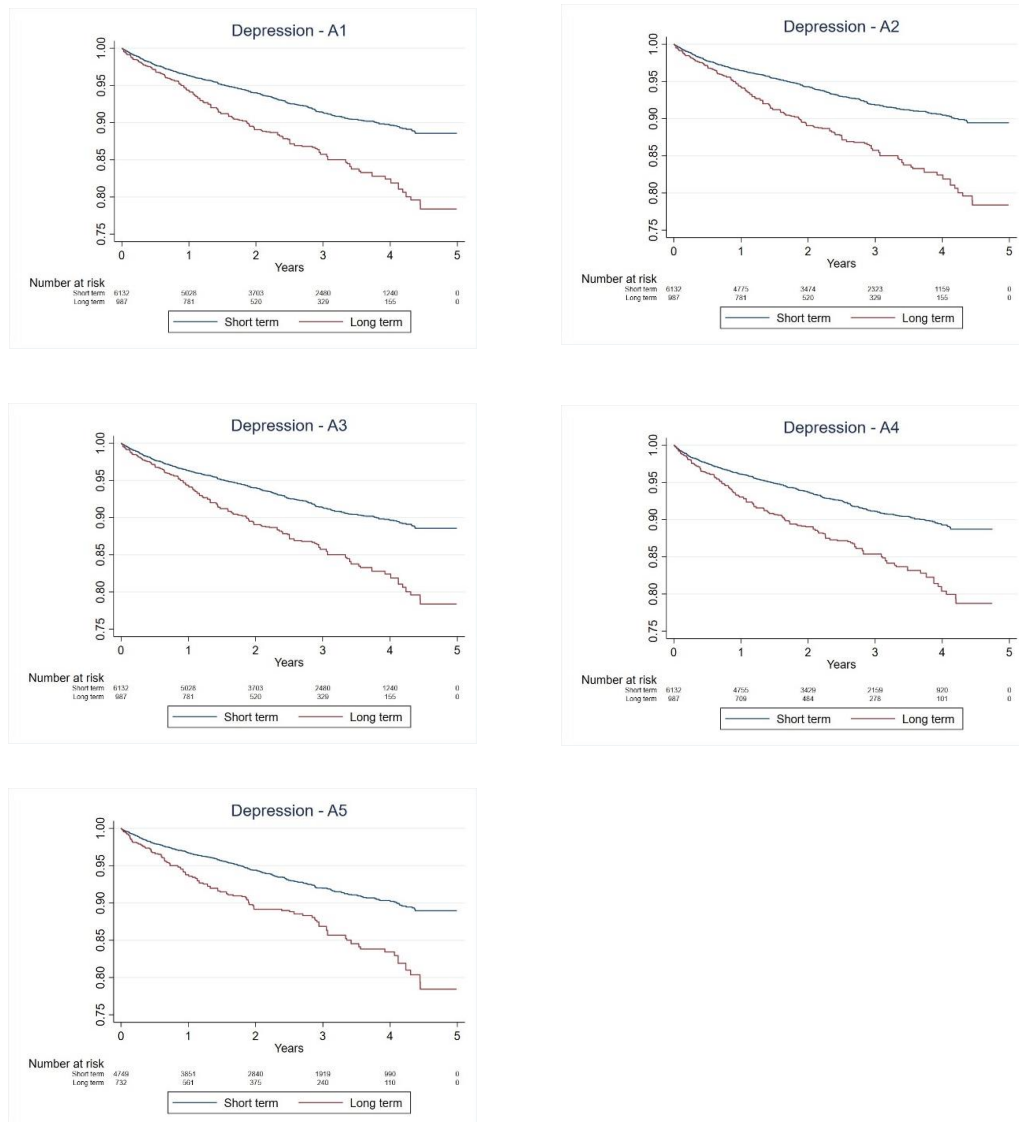
A3: Analysis with competing risk of death

A4: Analysis with outcomes since day 90

A5: Analysis using dispensation data and censoring short-term users if they initiate long-term opioids



**Figure S6. Kaplan Meier curves for depression, for each analysis for short-term and long-term users.**



A1: Main analysis

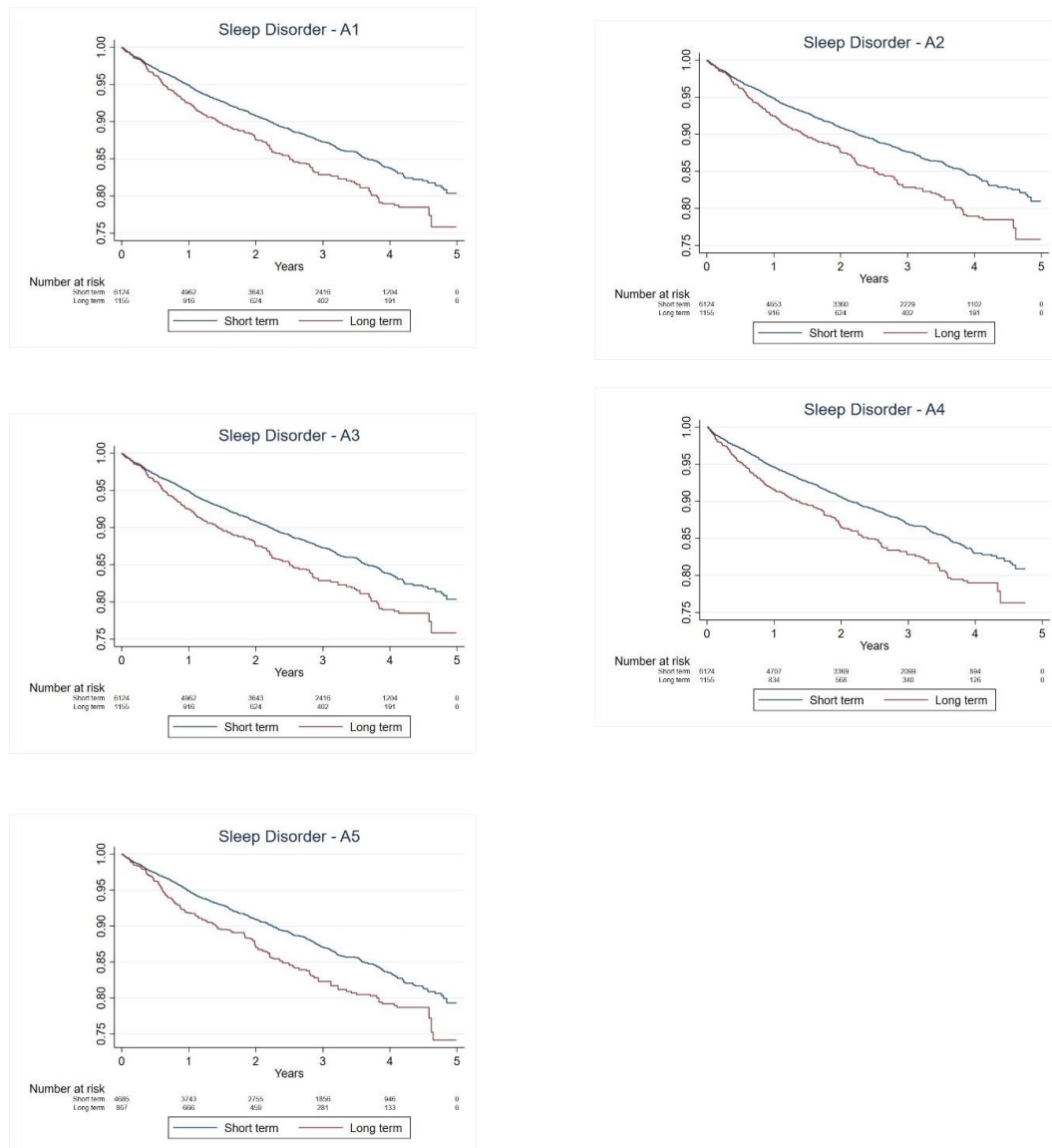
A2: Analysis censoring short-term users if they initiate long-term opioids

A3: Analysis with competing risk of death

A4: Analysis with outcomes since day 90

A5: Analysis using dispensation data and censoring short-term users if they initiate long-term opioids

**Figure S7. Kaplan Meier curves for sleep disorders, for short-term and long-term users.**



A1: Main analysis

A2: Analysis censoring short-term users if they initiate long-term opioids

A3: Analysis with competing risk of death

A4: Analysis with outcomes since day 90

A5: Analysis using dispensation data and censoring short-term users if they initiate long-term opioids

**Tables S8 to S22 present the results of the Cox regression models for each outcome and for the main and sensitivity analyses, following this order:**

A1: Main analysis

A2: Analysis censoring short-term users if they initiate long-term opioids

A3: Analysis with competing risk of death

A4: Analysis with outcomes since day 90

A5: Analysis using dispensation data and censoring short-term users if they initiate long-term opioids

**Table S8. Results of the regression model for the outcome of suicidal ideation, analysis A1.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.59	0.40	1.81	0.96	2.62	0.07
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	2.12	1.63	0.98	0.47	9.56	0.33
Tapentadol Long-acting	0.92	0.53	-0.15	0.30	2.82	0.88
Oxycodone Long-acting	0.74	0.63	-0.36	0.14	3.93	0.72
Buprenorphine Long-acting	0.00	0.00	-64.41	0.00	0.00	<0.001
Codeine	1.03	0.55	0.05	0.36	2.96	0.96
Age range, years						
18-44	1.00					
45-64	0.67	0.19	-1.46	0.39	1.15	0.14
65-74	0.37	0.20	-1.81	0.13	1.08	0.07
>=75	0.50	0.37	-0.95	0.12	2.09	0.34
Income level, euros/year						
<18.000	1.00					
18.000-100.000	0.44	0.24	-1.49	0.15	1.29	0.14
>100.000	0.00	0.00	-70.03	0.00	0.00	<0.001
No resources	1.19	0.39	0.53	0.62	2.27	0.60
Unknown	10.92	8.90	2.93	2.21	53.94	0.00
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	-1.01	0.99	1.00	0.31
Sex						
Men	0.98	0.37	-0.05	0.47	2.04	0.96
Comorbidities & lifestyle						
Ischemic cardiomyopathy	0.32	0.34	-1.07	0.04	2.59	0.29
COPD	1.06	0.57	0.11	0.37	3.02	0.91
Dementia	0.48	0.54	-0.65	0.05	4.41	0.51
Depression	1.20	0.33	0.65	0.69	2.06	0.52
Diabetes	1.11	0.41	0.28	0.54	2.29	0.78
Heart Failure	1.17	1.30	0.14	0.13	10.29	0.89
Hypertension	0.77	0.26	-0.77	0.40	1.49	0.44
Renal disease	1.14	0.74	0.20	0.32	4.06	0.84
Liver disease	1.20	0.46	0.48	0.56	2.56	0.63
Alcohol use	2.01	0.99	1.42	0.77	5.28	0.15
Tobacco use	1.62	0.47	1.68	0.92	2.85	0.09
Anxiety	2.96	1.20	2.67	1.33	6.55	0.01
Drug	0.86	0.50	-0.26	0.27	2.70	0.79
Personality disorders	0.86	0.46	-0.29	0.30	2.45	0.77
Psychotic disorders	1.17	0.44	0.43	0.57	2.44	0.67
Other psychiatric disorders	2.03	0.55	2.65	1.20	3.44	0.01
Sleep disorders	1.05	0.27	0.21	0.64	1.74	0.83
Previous suicidal ideation	1.00					
Overlapping medication						
Benzodiazepines	2.13	0.59	2.71	1.23	3.67	0.01
Gabapentinoids	2.01	0.69	2.04	1.03	3.93	0.04
Antipsychotics	2.64	1.07	2.38	1.19	5.85	0.02

**Table S9. Results of the regression model for the outcome of suicidal ideation, analysis A2.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.54	0.40	1.64	0.92	2.57	0.10
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	2.40	1.80	1.16	0.55	10.45	0.24
Tapentadol Long-acting	0.66	0.48	-0.58	0.16	2.71	0.56
Oxycodone Long-acting	0.83	0.70	-0.22	0.16	4.35	0.82
Buprenorphine Long-acting	0.00	0.00	-55.10	0.00	0.00	<0.001
Codeine	1.06	0.57	0.11	0.37	3.04	0.91
Age range, years						
18-44	1.00					
45-64	0.66	0.19	-1.44	0.38	1.16	0.15
65-74	0.36	0.20	-1.81	0.12	1.09	0.07
>=75	0.47	0.35	-1.02	0.11	2.01	0.31
Income level, euros/year						
<18.000	1.00					
18.000-100.000	0.48	0.26	-1.36	0.17	1.38	0.18
>100.000	0.00	0.00	-63.86	0.00	0.00	<0.001
No resources	1.05	0.37	0.13	0.52	2.11	0.89
Unknown	9.75	7.30	3.04	2.25	42.30	0.00
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	-1.00	0.99	1.00	0.32
Sex						
Men	0.85	0.34	-0.42	0.39	1.85	0.67
Comorbidities & lifestyle						
Ischemic cardiomyopathy	0.34	0.36	-1.02	0.04	2.73	0.31
COPD	1.21	0.65	0.35	0.42	3.47	0.72
Dementia	0.56	0.63	-0.52	0.06	5.06	0.61
Depression	1.20	0.34	0.63	0.68	2.10	0.53
Diabetes	1.18	0.44	0.43	0.57	2.44	0.67
Heart Failure	1.11	1.23	0.10	0.13	9.73	0.92
Hypertension	0.84	0.29	-0.50	0.43	1.65	0.61
Renal disease	1.15	0.75	0.21	0.31	4.16	0.84
Liver disease	1.32	0.50	0.73	0.63	2.79	0.46
Alcohol use	1.79	0.90	1.17	0.67	4.79	0.24
Tobacco use	1.59	0.47	1.57	0.89	2.85	0.12
Anxiety	2.75	1.13	2.48	1.24	6.14	0.01
Drug	1.23	0.64	0.40	0.45	3.40	0.69
Personality disorders	0.96	0.51	-0.09	0.34	2.71	0.93
Psychotic disorders	1.22	0.45	0.55	0.60	2.50	0.58
Other psychiatric disorders	2.18	0.57	3.00	1.31	3.62	0.00
Sleep disorders	1.05	0.28	0.20	0.63	1.76	0.84
Previous suicidal ideation	1.00					
Overlapping medication						
Benzodiazepines	2.04	0.58	2.52	1.17	3.55	0.01
Gabapentinoids	1.91	0.69	1.80	0.95	3.86	0.07
Antipsychotics	2.17	0.89	1.90	0.98	4.83	0.06

**Table S10. Results of the regression model for the outcome of suicidal ideation, analysis A3.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.59	0.41	1.80	0.96	2.61	0.07
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	2.11	1.62	0.97	0.47	9.51	0.33
Tapentadol Long-acting	0.92	0.53	-0.14	0.30	2.82	0.89
Oxycodone Long-acting	0.74	0.63	-0.35	0.14	3.94	0.73
Buprenorphine Long-acting	0.00	0.00	-20.80	0.00	0.00	<0.001
Codeine	1.03	0.55	0.05	0.36	2.96	0.96
Age range, years						
18-44	1.00					
45-64	0.67	0.19	-1.46	0.39	1.15	0.14
65-74	0.37	0.20	-1.82	0.13	1.08	0.07
>=75	0.48	0.35	-1.00	0.11	2.02	0.32
Income level, euros/year						
<18.000	1.00					
18.000-100.000	0.44	0.24	-1.50	0.15	1.29	0.13
>100.000	0.00	0.00	-22.83	0.00	0.00	<0.001
No resources	1.19	0.39	0.52	0.62	2.27	0.60
Unknown	10.40	8.59	2.83	2.06	52.51	0.01
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	-1.02	0.99	1.00	0.31
Sex						
Men	0.98	0.37	-0.06	0.47	2.03	0.95
Comorbidities & lifestyle						
Ischemic cardiomyopathy	0.32	0.34	-1.07	0.04	2.58	0.28
COPD	1.05	0.56	0.09	0.37	2.98	0.93
Dementia	0.45	0.51	-0.71	0.05	4.15	0.48
Depression	1.20	0.33	0.65	0.70	2.06	0.52
Diabetes	1.10	0.41	0.25	0.53	2.27	0.80
Heart Failure	1.09	1.22	0.08	0.12	9.75	0.94
Hypertension	0.77	0.26	-0.77	0.40	1.49	0.44
Renal disease	1.12	0.73	0.17	0.31	3.99	0.86
Liver disease	1.19	0.46	0.46	0.56	2.54	0.65
Alcohol use	2.02	0.99	1.43	0.77	5.30	0.15
Tobacco use	1.62	0.47	1.68	0.92	2.85	0.09
Anxiety	2.97	1.21	2.68	1.34	6.59	0.01
Drug	0.86	0.50	-0.26	0.27	2.70	0.79
Personality disorders	0.86	0.46	-0.28	0.30	2.46	0.78
Psychotic disorders	1.16	0.43	0.41	0.56	2.42	0.68
Other psychiatric disorders	2.04	0.54	2.66	1.21	3.44	0.01
Sleep disorders	1.06	0.27	0.21	0.64	1.74	0.83
Previous suicidal ideation	1.00					
Overlapping medication						
Benzodiazepines	2.12	0.59	2.72	1.23	3.66	0.01
Gabapentinoids	2.01	0.69	2.06	1.03	3.93	0.04
Antipsychotics	2.64	1.07	2.39	1.19	5.84	0.02

**Table S11. Results of the regression model for the outcome of suicidal ideation, analysis A4.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.80	0.48	2.19	1.06	3.04	0.03
Outcomes within 90 days						
Suicidal ideation	44.89	41.26	4.14	7.41	272.00	<0.001
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	2.49	1.95	1.17	0.54	11.57	0.24
Tapentadol Long-acting	1.11	0.67	0.17	0.34	3.64	0.86
Oxycodone Long-acting	0.87	0.74	-0.17	0.16	4.64	0.87
Buprenorphine Long-acting	0.00	0.00	-63.20	0.00	0.00	<0.001
Codeine	1.17	0.65	0.28	0.39	3.46	0.78
Age range, years						
18-44	1.00					
45-64	0.53	0.16	-2.13	0.29	0.95	0.03
65-74	0.36	0.20	-1.81	0.12	1.09	0.07
>=75	0.53	0.40	-0.85	0.12	2.30	0.40
Income level, euros/year						
<18.000	1.00					
18.000-100.000	0.56	0.30	-1.06	0.19	1.63	0.29
>100.000	0.00	0.00	-60.67	0.00	0.00	<0.001
No resources	1.30	0.45	0.74	0.65	2.56	0.46
Unknown	13.38	9.98	3.48	3.10	57.70	<0.001
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	-0.96	0.99	1.00	0.34
Sex						
Men	0.76	0.33	-0.62	0.33	1.79	0.54
Comorbidities & lifestyle						
Ischemic cardiomyopathy	0.35	0.37	-0.98	0.04	2.85	0.33
COPD	1.19	0.64	0.33	0.42	3.42	0.74
Dementia	0.56	0.65	-0.50	0.06	5.48	0.62
Depression	1.27	0.37	0.83	0.72	2.25	0.41
Diabetes	1.06	0.41	0.15	0.49	2.27	0.88
Heart Failure	1.33	1.47	0.25	0.15	11.71	0.80
Hypertension	0.92	0.33	-0.23	0.45	1.87	0.82
Renal disease	0.73	0.59	-0.39	0.15	3.60	0.70
Liver disease	1.40	0.55	0.87	0.65	3.03	0.39
Alcohol use	2.48	1.26	1.78	0.91	6.70	0.08
Tobacco use	1.87	0.58	2.00	1.01	3.44	0.05
Anxiety	4.21	1.94	3.12	1.71	10.39	0.00
Drug	1.02	0.61	0.03	0.32	3.28	0.98
Personality disorders	1.11	0.63	0.19	0.37	3.35	0.85
Psychotic disorders	1.05	0.47	0.12	0.44	2.51	0.91
Other psychiatric disorders	1.69	0.52	1.71	0.93	3.08	0.09
Sleep disorders	0.94	0.26	-0.23	0.55	1.62	0.82
Previous suicidal ideation	1.00					
Overlapping medication						
Benzodiazepines	1.78	0.50	2.06	1.03	3.09	0.04
Gabapentinoids	2.09	0.75	2.05	1.03	4.23	0.04
Antipsychotics	2.13	1.07	1.52	0.80	5.69	0.13

**Table S12. Results of the regression model for the outcome of suicidal ideation, analysis A5.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.64	0.53	1.54	0.87	3.09	0.12
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	1.78	2.17	0.48	0.16	19.33	0.63
Tapentadol Long-acting	0.91	0.74	-0.12	0.18	4.49	0.90
Oxycodone Long-acting	0.76	0.83	-0.25	0.09	6.54	0.80
Buprenorphine Long-acting	0.00	0.00	-33.60	0.00	0.00	<0.001
Codeine	0.97	0.61	-0.04	0.29	3.30	0.97
Age range, years						
18-44	1.00					
45-64	0.91	0.32	-0.26	0.46	1.81	0.79
65-74	0.19	0.17	-1.88	0.04	1.08	0.06
>=75	0.16	0.19	-1.56	0.02	1.59	0.12
Income level, euros/year						
<18.000	1.00					
18.000-100.000	0.32	0.23	-1.57	0.08	1.33	0.12
>100.000	0.00					
No resources	0.79	0.35	-0.52	0.33	1.91	0.60
Unknown	14.65	12.59	3.12	2.72	78.98	0.00
Daily Morphine Milligram Equivalent						
Daily MME	0.99	0.01	-0.90	0.98	1.01	0.37
Sex						
Men	1.01	0.51	0.02	0.37	2.74	0.98
Comorbidities & lifestyle						
Ischemic cardiomyopathy	0.33	0.37	-1.00	0.04	2.85	0.32
COPD	1.68	0.97	0.90	0.54	5.19	0.37
Dementia	0.77	0.91	-0.22	0.08	7.86	0.83
Depression	1.05	0.36	0.14	0.53	2.05	0.89
Diabetes	1.46	0.65	0.86	0.61	3.49	0.39
Heart Failure	0.00	0.00	-82.25	0.00	0.00	<0.001
Hypertension	0.88	0.32	-0.35	0.44	1.79	0.73
Renal disease	1.97	1.29	1.03	0.54	7.12	0.30
Liver disease	0.83	0.44	-0.36	0.30	2.32	0.72
Alcohol use	2.33	1.31	1.51	0.78	6.99	0.13
Tobacco use	1.40	0.49	0.97	0.71	2.78	0.33
Anxiety	1.59	0.78	0.95	0.61	4.16	0.34
Drug	0.80	0.59	-0.31	0.19	3.42	0.76
Personality disorders	1.22	0.68	0.35	0.41	3.61	0.73
Psychotic disorders	1.86	0.79	1.46	0.81	4.27	0.14
Other psychiatric disorders	1.89	0.65	1.85	0.96	3.69	0.06
Sleep disorders	1.12	0.36	0.36	0.60	2.11	0.72
Previous suicidal ideation	1.00					
Overlapping medication						
Benzodiazepines	2.27	0.80	2.34	1.14	4.53	0.02
Gabapentinoids	1.87	0.87	1.34	0.75	4.65	0.18
Antipsychotics	2.41	1.20	1.77	0.91	6.40	0.08



**Table S13. Results of the regression model for the outcome of sleep disorders, analysis A1.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.30	0.12	2.88	1.09	1.55	0.00
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	1.32	0.45	0.81	0.68	2.56	0.42
Tapentadol Long-acting	1.42	0.22	2.31	1.05	1.91	0.02
Oxycodone Long-acting	1.16	0.24	0.72	0.77	1.75	0.47
Buprenorphine Long-acting	1.48	0.64	0.90	0.63	3.47	0.37
Codeine	0.97	0.15	-0.18	0.72	1.32	0.86
Age range, years						
18-44	1.00					
45-64	1.21	0.12	1.93	1.00	1.46	0.05
65-74	1.27	0.16	1.90	0.99	1.62	0.06
>=75	1.12	0.16	0.78	0.84	1.49	0.43
Income level, euros/year						
<18.000	1.00					
18.000-100.000	0.94	0.09	-0.67	0.77	1.13	0.50
>100.000	0.00	0.00	-	0.00	0.00	<0.001
No resources	1.18	0.13	1.43	0.94	1.47	0.15
Unknown	0.61	0.46	-0.66	0.14	2.66	0.51
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	-1.24	1.00	1.00	0.22
Sex						
Men	1.02	0.09	0.25	0.86	1.22	0.81
Comorbidities & lifestyle						
Ischemic cardiomyopathy	1.44	0.22	2.46	1.08	1.93	0.01
COPD	1.47	0.21	2.76	1.12	1.93	0.01
Dementia	1.31	0.27	1.31	0.87	1.96	0.19
Depression	1.13	0.10	1.32	0.94	1.34	0.19
Diabetes	1.13	0.12	1.17	0.92	1.38	0.24
Heart Failure	1.32	0.28	1.27	0.86	2.01	0.20
Hypertension	1.13	0.10	1.39	0.95	1.33	0.16
Renal disease	1.07	0.16	0.46	0.80	1.44	0.64
Liver disease	0.98	0.13	-0.17	0.76	1.26	0.87
Alcohol use	1.51	0.33	1.91	0.99	2.30	0.06
Tobacco use	0.99	0.10	-0.06	0.81	1.22	0.95
Anxiety	1.15	0.10	1.68	0.98	1.35	0.09
Drug	0.85	0.26	-0.56	0.47	1.53	0.58
Personality disorders	0.73	0.22	-1.02	0.41	1.33	0.31
Psychotic disorders	1.04	0.15	0.28	0.79	1.38	0.78
Other psychiatric disorders	1.16	0.13	1.32	0.93	1.43	0.19
Sleep disorders	1.00					
Previous suicidal ideation	2.95	1.38	2.32	1.18	7.36	0.02
Overlapping medication						
Benzodiazepines	1.14	0.09	1.53	0.97	1.34	0.13
Gabapentinoids	1.07	0.14	0.51	0.82	1.40	0.61
Antipsychotics	0.67	0.16	-1.65	0.41	1.08	0.10

**Table S14. Results of the regression model for the outcome of sleep disorders, analysis A2.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.32	0.12	3.03	1.10	1.58	0.00
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	1.42	0.47	1.05	0.74	2.72	0.29
Tapentadol Long-acting	1.49	0.23	2.59	1.10	2.02	0.01
Oxycodone Long-acting	1.29	0.27	1.24	0.86	1.94	0.22
Buprenorphine Long-acting	1.52	0.66	0.97	0.65	3.55	0.33
Codeine	0.97	0.15	-0.18	0.71	1.32	0.85
Age range, years						
18-44	1.00					
45-64	1.24	0.13	2.18	1.02	1.52	0.03
65-74	1.29	0.17	1.96	1.00	1.66	0.05
>=75	1.16	0.17	1.00	0.87	1.56	0.32
Income level, euros/year						
<18.000	1.00					
18.000-100.000	0.91	0.09	-0.89	0.75	1.12	0.37
>100.000	0.00	0.00	-	0.00	0.00	<0.001
No resources	1.17	0.14	123.83	1.29	0.92	0.20
Unknown	0.73	0.54	-0.42	0.17	3.13	0.68
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	-0.89	1.00	1.00	0.37
Sex						
Men	1.04	0.10	0.37	0.86	1.24	0.71
Comorbidities & lifestyle						
Ischemic cardiomyopathy	1.46	0.22	2.46	1.08	1.97	0.01
COPD	1.47	0.21	2.69	1.11	1.95	0.01
Dementia	1.30	0.28	1.23	0.86	1.98	0.22
Depression	1.14	0.11	1.36	0.95	1.36	0.17
Diabetes	1.04	0.11	0.37	0.84	1.29	0.71
Heart Failure	1.38	0.31	1.44	0.89	2.12	0.15
Hypertension	1.11	0.10	1.14	0.93	1.31	0.26
Renal disease	1.01	0.16	0.08	0.74	1.38	0.94
Liver disease	0.97	0.13	-0.22	0.75	1.26	0.82
Alcohol use	1.49	0.34	1.77	0.96	2.31	0.08
Tobacco use	0.95	0.10	-0.52	0.76	1.17	0.60
Anxiety	1.14	0.10	1.57	0.97	1.35	0.12
Drug	0.91	0.29	-0.31	0.49	1.69	0.76
Personality disorders	0.67	0.23	-1.17	0.35	1.31	0.24
Psychotic disorders	0.98	0.15	-0.15	0.72	1.32	0.88
Other psychiatric disorders	1.16	0.13	1.30	0.93	1.45	0.20
Sleep disorders	1.00					
Previous suicidal ideation	3.42	1.60	2.63	1.37	8.54	0.01
Overlapping medication						
Benzodiazepines	1.12	0.10	1.35	0.95	1.33	0.18
Gabapentinoids	1.15	0.16	0.99	0.87	1.50	0.32
Antipsychotics	0.58	0.16	-1.97	0.33	1.00	0.05

**Table S15. Results of the regression model for the outcome of sleep disorders, analysis A3.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.30	0.12	2.85	1.08	1.55	0.00
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	1.21	0.41	0.55	0.62	2.34	0.58
Tapentadol Long-acting	1.43	0.22	2.37	1.06	1.93	0.02
Oxycodone Long-acting	1.17	0.25	0.74	0.77	1.76	0.46
Buprenorphine Long-acting	1.46	0.63	0.87	0.62	3.42	0.39
Codeine	0.97	0.15	-0.20	0.72	1.31	0.84
Age range, years						
18-44	1.00					
45-64	1.21	0.12	1.95	1.00	1.46	0.05
65-74	1.27	0.16	1.89	0.99	1.62	0.06
>=75	1.08	0.16	0.54	0.81	1.44	0.59
Income level, euros/year						
<18.000	1.00					
18.000-100.000	0.93	0.09	-0.72	0.77	1.13	0.47
>100.000	0.00	0.00	-53.10	0.00	0.00	<0.001
No resources	1.17	0.13	1.36	0.93	1.46	0.17
Unknown	0.61	0.46	-0.66	0.14	2.64	0.51
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	-1.22	1.00	1.00	0.22
Sex						
Men	1.01	0.09	0.11	0.85	1.20	0.91
Comorbidities & lifestyle						
Ischemic cardiomyopathy	1.44	0.22	2.45	1.08	1.93	0.01
COPD	1.44	0.20	2.64	1.10	1.90	0.01
Dementia	1.25	0.26	1.07	0.83	1.88	0.28
Depression	1.12	0.10	1.30	0.94	1.34	0.19
Diabetes	1.12	0.12	1.10	0.92	1.37	0.27
Heart Failure	1.16	0.26	0.68	0.75	1.79	0.50
Hypertension	1.12	0.10	1.37	0.95	1.33	0.17
Renal disease	1.05	0.16	0.30	0.78	1.40	0.77
Liver disease	0.97	0.12	-0.26	0.75	1.24	0.80
Alcohol use	1.54	0.33	2.00	1.01	2.34	0.05
Tobacco use	0.99	0.10	-0.06	0.81	1.21	0.95
Anxiety	1.16	0.10	1.75	0.98	1.36	0.08
Drug	0.83	0.25	-0.62	0.46	1.50	0.53
Personality disorders	0.73	0.22	-1.02	0.41	1.33	0.31
Psychotic disorders	1.03	0.15	0.17	0.77	1.36	0.86
Other psychiatric disorders	1.16	0.13	1.33	0.93	1.43	0.18
Sleep disorders	1.00					
Previous suicidal ideation	2.91	1.37	2.28	1.16	7.31	0.02
Overlapping medication						
Benzodiazepines	1.14	0.09	1.55	0.97	1.34	0.12
Gabapentinoids	1.08	0.15	0.57	0.83	1.41	0.57
Antipsychotics	0.65	0.16	-1.73	0.40	1.06	0.08

**Table S16. Results of the regression model for the outcome of sleep disorders, analysis A4.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.38	0.13	3.49	1.15	1.66	<0.001
Outcomes within 90 days						
Sleep disorders	7.70	1.27	12.38	5.57	10.64	<0.001
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	1.48	0.49	1.17	0.77	2.85	0.24
Tapentadol Long-acting	1.33	0.21	1.78	0.97	1.82	0.07
Oxycodone Long-acting	1.27	0.27	1.14	0.84	1.93	0.26
Buprenorphine Long-acting	1.70	0.77	1.17	0.70	4.11	0.24
Codeine	1.00	0.16	-0.03	0.73	1.36	0.98
Age range, years						
18-44	1.00					
45-64	1.10	0.11	0.95	0.90	1.34	0.34
65-74	1.24	0.16	1.70	0.97	1.60	0.09
>=75	1.04	0.16	0.25	0.77	1.40	0.80
Income level, euros/year						
<18.000	1.00					
18.000-100.000	0.93	0.10	-0.74	0.76	1.13	0.46
>100.000	0.00	0.00	-	0.00	0.00	<0.001
No resources	1.18	0.14	112.60 1.42	0.94	1.49	0.16
Unknown	0.30	0.31	-1.17	0.04	2.28	0.24
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	-1.26	0.99	1.00	0.21
Sex						
Men	1.04	0.10	0.44	0.87	1.25	0.66
Comorbidities & lifestyle						
Ischemic cardiomyopathy	1.42	0.22	2.27	1.05	1.93	0.02
COPD	1.23	0.19	1.35	0.91	1.66	0.18
Dementia	1.27	0.27	1.13	0.84	1.93	0.26
Depression	1.18	0.11	1.83	0.99	1.41	0.07
Diabetes	1.28	0.13	2.36	1.04	1.57	0.02
Heart Failure	1.22	0.28	0.86	0.78	1.91	0.39
Hypertension	1.15	0.10	1.64	0.97	1.37	0.10
Renal disease	0.96	0.15	-0.29	0.70	1.30	0.77
Liver disease	0.87	0.12	-1.02	0.66	1.14	0.31
Alcohol use	1.67	0.38	2.24	1.07	2.60	0.03
Tobacco use	1.04	0.11	0.38	0.84	1.29	0.70
Anxiety	1.13	0.10	1.42	0.95	1.34	0.16
Drug	0.97	0.30	-0.09	0.53	1.77	0.93
Personality disorders	0.62	0.22	-1.35	0.31	1.24	0.18
Psychotic disorders	1.06	0.16	0.36	0.79	1.42	0.72
Other psychiatric disorders	1.16	0.14	1.24	0.92	1.46	0.21
Sleep disorders	1.00					
Previous suicidal ideation	2.07	1.24	1.22	0.64	6.69	0.22
Overlapping medication						
Benzodiazepines	1.11	0.10	1.22	0.94	1.32	0.22
Gabapentinoids	1.18	0.16	1.23	0.90	1.55	0.22
Antipsychotics	0.59	0.17	-1.81	0.34	1.04	0.07

**Table S17. Results of the regression model for the outcome of sleep disorders, analysis A5.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.30	0.14	2.37	1.05	1.61	0.02
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	0.94	0.42	-0.14	0.39	2.25	0.89
Tapentadol Long-acting	1.59	0.56	1.32	0.80	3.19	0.19
Oxycodone Long-acting	1.35	0.29	1.39	0.88	2.05	0.17
Buprenorphine Long-acting	1.42	0.77	0.65	0.49	4.09	0.52
Codeine	1.01	0.17	0.06	0.73	1.39	0.95
Age range, years						
18-44	1.00					
45-64	1.14	0.13	1.18	0.92	1.43	0.24
65-74	1.23	0.18	1.40	0.92	1.63	0.16
>=75	1.23	0.20	1.28	0.89	1.70	0.20
Income level, euros/year						
<18.000	1.00					
18.000-100.000	0.84	0.10	-1.48	0.67	1.06	0.14
>100.000	0.00	0.00	-66.85	0.00	0.00	<0.001
No resources	1.16	0.15	1.11	0.90	1.49	0.27
Unknown	0.92	0.73	-0.11	0.20	4.32	0.91
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	-1.11	1.00	1.00	0.27
Sex						
Men	0.91	0.10	-0.90	0.74	1.12	0.37
Comorbidities & lifestyle						
Ischemic cardiomyopathy	1.29	0.22	1.51	0.93	1.79	0.13
COPD	1.55	0.24	2.80	1.14	2.10	0.01
Dementia	1.47	0.35	1.64	0.93	2.33	0.10
Depression	1.11	0.11	1.00	0.91	1.36	0.32
Diabetes	1.24	0.14	1.84	0.99	1.55	0.07
Heart Failure	1.53	0.33	1.97	1.00	2.34	0.05
Hypertension	1.12	0.11	1.14	0.92	1.36	0.25
Renal disease	1.03	0.18	0.17	0.73	1.45	0.87
Liver disease	1.03	0.15	0.21	0.77	1.37	0.83
Alcohol use	1.54	0.37	1.77	0.96	2.48	0.08
Tobacco use	1.11	0.13	0.89	0.88	1.39	0.37
Anxiety	1.15	0.11	1.46	0.95	1.38	0.14
Drug	0.54	0.21	-1.61	0.25	1.14	0.11
Personality disorders	1.07	0.31	0.23	0.61	1.89	0.81
Psychotic disorders	0.86	0.15	-0.91	0.61	1.20	0.36
Other psychiatric disorders	1.29	0.16	2.09	1.02	1.64	0.04
Sleep disorders	1.00					
Previous suicidal ideation	3.21	1.69	2.21	1.14	9.01	0.03
Overlapping medication						
Benzodiazepines	1.03	0.10	0.31	0.86	1.24	0.76
Gabapentinoids	1.07	0.16	0.45	0.79	1.45	0.65
Antipsychotics	0.95	0.24	-0.22	0.58	1.54	0.83

**Table S18. Results of the regression model for the outcome of depression, analysis A1.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.59	0.17	4.36	1.29	1.95	<0.001
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	0.90	0.51	-0.19	0.30	2.72	0.85
Tapentadol Long-acting	1.60	0.28	2.75	1.15	2.24	0.01
Oxycodone Long-acting	1.80	0.43	2.48	1.13	2.86	0.01
Buprenorphine Long-acting	1.72	0.80	1.17	0.69	4.29	0.24
Codeine	0.94	0.19	-0.32	0.64	1.38	0.75
Age range, years						
18-44	1.00					
45-64	1.13	0.14	1.05	0.90	1.43	0.29
65-74	0.90	0.15	-0.65	0.65	1.24	0.52
>=75	0.95	0.18	-0.28	0.65	1.37	0.78
Income level, euros/year						
<18.000	1.00					
18.000-100.000	1.02	0.13	0.16	0.80	1.30	0.87
>100.000	0.42	0.42	-0.87	0.06	2.91	0.38
No resources	0.78	0.12	-1.58	0.57	1.06	0.12
Unknown	1.78	1.13	0.91	0.51	6.20	0.36
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	0.76	1.00	1.00	0.45
Sex						
Men	0.53	0.06	-5.25	0.42	0.67	<0.001
Comorbidities & lifestyle						
Ischemic cardiomyopathy	1.06	0.22	0.29	0.71	1.58	0.77
COPD	1.48	0.25	2.32	1.06	2.07	0.02
Dementia	2.10	0.54	2.86	1.26	3.48	0.00
Depression	1.00					
Diabetes	1.10	0.14	0.73	0.85	1.42	0.47
Heart Failure	1.56	0.39	1.77	0.95	2.54	0.08
Hypertension	0.96	0.10	-0.42	0.78	1.18	0.67
Renal disease	0.96	0.20	-0.19	0.64	1.44	0.85
Liver disease	1.06	0.16	0.36	0.78	1.42	0.72
Alcohol use	0.96	0.30	-0.11	0.52	1.79	0.91
Tobacco use	1.09	0.13	0.67	0.85	1.39	0.50
Anxiety	1.35	0.13	3.23	1.13	1.63	0.00
Drug	1.94	0.68	1.89	0.98	3.86	0.06
Personality disorders	1.40	0.50	0.95	0.70	2.82	0.34
Psychotic disorders	0.72	0.20	-1.19	0.41	1.24	0.23
Other psychiatric disorders	1.65	0.20	4.06	1.30	2.10	<0.001
Sleep disorders	1.22	0.12	2.00	1.00	1.48	0.05
Previous suicidal ideation	0.30	0.31	-1.18	0.04	2.19	0.24
Overlapping medication						
Benzodiazepines	1.74	0.16	5.84	1.44	2.09	<0.001
Gabapentinoids	1.26	0.21	1.39	0.91	1.76	0.16
Antipsychotics	1.23	0.35	0.74	0.71	2.15	0.46

**Table S19. Results of the regression model for the outcome of depression, analysis A2.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.68	0.18	4.84	1.36	2.08	<0.001
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	0.98	0.57	-0.03	0.32	3.03	0.97
Tapentadol Long-acting	1.52	0.28	2.28	1.06	2.18	0.02
Oxycodone Long-acting	1.93	0.46	2.78	1.21	3.07	0.01
Buprenorphine Long-acting	1.38	0.75	0.59	0.47	4.01	0.56
Codeine	0.93	0.19	-0.35	0.62	1.39	0.73
Age range, years						
18-44	1.00					
45-64	1.16	0.14	1.16	0.91	1.47	0.25
65-74	0.96	0.16	-0.26	0.68	1.34	0.80
>=75	1.01	0.20	0.07	0.69	1.50	0.95
Income level, euros/year						
<18.000	1.00					
18.000-100.000	1.01	0.13	0.09	0.79	1.30	0.93
>100.000	0.49	0.48	-0.73	0.07	3.34	0.47
No resources	0.73	0.13	-1.87	0.52	1.02	0.06
Unknown	2.30	1.41	1.36	0.69	7.68	0.18
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	1.30	1.00	1.01	0.19
Sex						
Men	0.57	0.07	-4.59	0.45	0.73	<0.001
Comorbidities & lifestyle						
Ischemic cardiomyopathy	1.06	0.22	0.28	0.70	1.61	0.78
COPD	1.53	0.27	2.42	1.08	2.15	0.02
Dementia	1.95	0.53	2.45	1.14	3.31	0.01
Depression	1.00					
Diabetes	1.00	0.14	-0.01	0.76	1.32	1.00
Heart Failure	1.47	0.39	1.46	0.88	2.46	0.15
Hypertension	0.97	0.11	-0.30	0.78	1.20	0.77
Renal disease	0.96	0.21	-0.19	0.63	1.46	0.85
Liver disease	1.06	0.17	0.38	0.78	1.45	0.71
Alcohol use	1.02	0.32	0.06	0.55	1.90	0.95
Tobacco use	1.06	0.14	0.43	0.82	1.37	0.67
Anxiety	1.42	0.14	3.54	1.17	1.72	<0.001
Drug	1.80	0.68	1.56	0.86	3.80	0.12
Personality disorders	1.28	0.51	0.62	0.59	2.79	0.54
Psychotic disorders	0.75	0.22	-0.97	0.43	1.33	0.33
Other psychiatric disorders	1.64	0.21	3.81	1.27	2.11	<0.001
Sleep disorders	1.20	0.12	1.73	0.98	1.46	0.08
Previous suicidal ideation	0.30	0.30	-1.19	0.04	2.16	0.23
Overlapping medication						
Benzodiazepines	1.67	0.17	5.15	1.37	2.02	<0.001
Gabapentinoids	1.22	0.22	1.09	0.85	1.73	0.28
Antipsychotics	1.26	0.37	0.79	0.71	2.23	0.43

**Table S20. Results of the regression model for the outcome of depression, analysis A3.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.58	0.17	4.31	1.28	1.94	<0.001
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	0.89	0.49	-0.21	0.30	2.64	0.83
Tapentadol Long-acting	1.61	0.28	2.78	1.15	2.26	0.01
Oxycodone Long-acting	1.78	0.42	2.42	1.12	2.83	0.02
Buprenorphine Long-acting	1.68	0.79	1.11	0.67	4.20	0.27
Codeine	0.93	0.19	-0.34	0.63	1.38	0.73
Age range, years						
18-44	1.00					
45-64	1.13	0.14	1.06	0.90	1.43	0.29
65-74	0.90	0.15	-0.65	0.65	1.24	0.52
>=75	0.92	0.18	-0.46	0.63	1.33	0.64
Income level, euros/year						
<18.000	1.00					
18.000-100.000	1.02	0.13	0.16	0.80	1.30	0.87
>100.000	0.43	0.42	-0.87	0.06	2.93	0.39
No resources	0.78	0.12	-1.59	0.57	1.06	0.11
Unknown	1.82	1.15	0.95	0.53	6.26	0.34
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	0.69	1.00	1.00	0.49
Sex						
Men	0.52	0.06	-5.38	0.41	0.66	<0.001
Comorbidities & lifestyle						
Ischemic cardiomyopathy	1.08	0.22	0.36	0.72	1.60	0.72
COPD	1.47	0.25	2.27	1.05	2.05	0.02
Dementia	1.98	0.52	2.60	1.18	3.31	0.01
Depression	1.00					
Diabetes	1.09	0.14	0.67	0.84	1.41	0.50
Heart Failure	1.40	0.35	1.34	0.86	2.29	0.18
Hypertension	0.95	0.10	-0.44	0.77	1.18	0.66
Renal disease	0.94	0.19	-0.31	0.63	1.40	0.75
Liver disease	1.04	0.16	0.27	0.77	1.41	0.78
Alcohol use	0.98	0.31	-0.06	0.53	1.83	0.95
Tobacco use	1.09	0.13	0.68	0.85	1.39	0.50
Anxiety	1.35	0.13	3.23	1.13	1.63	0.00
Drug	1.98	0.69	1.95	1.00	3.93	0.05
Personality disorders	1.39	0.50	0.93	0.69	2.80	0.35
Psychotic disorders	0.70	0.20	-1.24	0.40	1.23	0.22
Other psychiatric disorders	1.66	0.20	4.12	1.30	2.11	<0.001
Sleep disorders	1.21	0.12	1.97	1.00	1.47	0.05
Previous suicidal ideation	0.31	0.31	-1.16	0.04	2.24	0.25
Overlapping medication						
Benzodiazepines	1.75	0.16	5.91	1.45	2.10	<0.001
Gabapentinoids	1.27	0.21	1.43	0.92	1.77	0.15
Antipsychotics	1.19	0.34	0.59	0.68	2.08	0.55



**Table S21. Results of the regression model for the outcome of depression, analysis A4.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
Group						
Long-term use	1.64	0.18	4.45	1.32	2.03	<0.001
Outcomes within 90 days						
Sleep disorders	18.25	3.58	14.78	12.42	26.82	<0.001
Opioid						
Tramadol	1.00					
Fentanyl Long-acting	1.16	0.65	0.27	0.39	3.48	0.79
Tapentadol Long-acting	1.58	0.27	2.64	1.13	2.21	0.01
Oxycodone Long-acting	2.15	0.51	3.22	1.35	3.42	0.00
Buprenorphine Long-acting	1.69	0.72	1.24	0.74	3.91	0.22
Codeine	1.00	0.21	0.01	0.67	1.50	0.99
Age range, years						
18-44	1.00					
45-64	1.09	0.14	0.66	0.85	1.39	0.51
65-74	0.81	0.14	-1.24	0.58	1.13	0.21
>=75	0.90	0.17	-0.55	0.62	1.31	0.58
Income level, euros/year						
<18.000	1.00					
18.000-100.000	1.08	0.14	0.61	0.84	1.39	0.54
>100.000	0.48	0.48	-0.74	0.07	3.36	0.46
No resources	0.76	0.14	-1.52	0.53	1.08	0.13
Unknown	2.00	1.14	1.22	0.65	6.09	0.22
Daily Morphine Milligram Equivalent						
Daily MME	1.00	0.00	0.83	1.00	1.00	0.41
Sex						
Men	0.46	0.06	-5.88	0.36	0.60	<0.001
Comorbidities & lifestyle						
Ischemic cardiomyopathy	1.06	0.24	0.24	0.68	1.65	0.81
COPD	1.31	0.27	1.34	0.88	1.96	0.18
Dementia	2.58	0.69	3.51	1.52	4.37	<0.001
Depression	1.00					
Diabetes	1.12	0.15	0.83	0.86	1.46	0.40
Heart Failure	1.19	0.35	0.60	0.67	2.13	0.55
Hypertension	1.06	0.12	0.52	0.85	1.32	0.60
Renal disease	0.96	0.19	-0.23	0.65	1.41	0.82
Liver disease	1.11	0.17	0.65	0.81	1.51	0.52
Alcohol use	1.20	0.39	0.55	0.63	2.26	0.58
Tobacco use	1.24	0.15	1.71	0.97	1.58	0.09
Anxiety	1.30	0.13	2.67	1.07	1.58	0.01
Drug	1.45	0.51	1.05	0.73	2.88	0.29
Personality disorders	1.63	0.61	1.31	0.78	3.38	0.19
Psychotic disorders	0.58	0.18	-1.77	0.32	1.06	0.08
Other psychiatric disorders	1.43	0.20	2.57	1.09	1.88	0.01
Sleep disorders	1.11	0.12	0.97	0.90	1.38	0.33
Previous suicidal ideation	0.42	0.43	-0.86	0.06	3.04	0.39
Overlapping medication						
Benzodiazepines	1.55	0.16	4.27	1.27	1.89	<0.001
Gabapentinoids	1.21	0.25	0.91	0.80	1.81	0.36
Antipsychotics	1.60	0.46	1.63	0.91	2.82	0.10

**Table S22. Results of the regression model for the outcome of depression, analysis A5.**

variable	Hazard ratio	SE	Z	Lower interval	Upper interval	Pvalue
<b>Group</b>						
Long-term use	1.56	0.21	3.30	1.20	2.02	<0.001
<b>Opioid</b>						
Tramadol	1.00					
Fentanyl Long-acting	1.09	0.69	0.14	0.32	3.75	0.89
Tapentadol Long-acting	2.74	0.92	2.99	1.42	5.31	0.00
Oxycodone Long-acting	2.36	0.60	3.36	1.43	3.88	<0.001
Buprenorphine Long-acting	0.54	0.48	-0.70	0.10	3.03	0.49
Codeine	0.88	0.20	-0.56	0.57	1.36	0.58
<b>Age range, years</b>						
18-44	1.00					
45-64	1.11	0.15	0.75	0.84	1.46	0.45
65-74	0.96	0.18	-0.21	0.66	1.39	0.84
>=75	1.00	0.22	-0.01	0.65	1.53	0.99
<b>Income level, euros/year</b>						
<18.000	1.00					
18.000-100.000	1.12	0.16	0.83	0.85	1.48	0.41
>100.000	-					
No resources	0.70	0.13	-1.85	0.48	1.02	0.06
Unknown	3.99	2.79	1.98	1.02	15.71	0.05
<b>Daily Morphine Milligram Equivalent</b>						
Daily MME	1.00	0.00	0.25	1.00	1.01	0.80
<b>Sex</b>						
Men	0.49	0.07	-4.94	0.37	0.65	<0.001
<b>Comorbidities &amp; lifestyle</b>						
Ischemic cardiomyopathy	1.14	0.26	0.56	0.73	1.77	0.57
COPD	1.56	0.31	2.24	1.06	2.31	0.03
Dementia	2.20	0.72	2.42	1.16	4.18	0.02
Depression	1.00					
Diabetes	1.18	0.18	1.09	0.87	1.60	0.28
Heart Failure	1.19	0.34	0.62	0.68	2.08	0.54
Hypertension	0.89	0.11	-0.89	0.70	1.14	0.37
Renal disease	0.93	0.24	-0.27	0.57	1.54	0.79
Liver disease	1.15	0.20	0.79	0.82	1.61	0.43
Alcohol use	1.21	0.43	0.53	0.60	2.44	0.60
Tobacco use	1.04	0.15	0.24	0.77	1.39	0.81
Anxiety	1.52	0.17	3.73	1.22	1.89	<0.001
Drug	2.05	0.91	1.61	0.86	4.91	0.11
Personality disorders	1.47	0.61	0.93	0.65	3.32	0.35
Psychotic disorders	0.71	0.25	-0.95	0.35	1.43	0.34
Other psychiatric disorders	1.77	0.25	3.99	1.34	2.34	<0.001
Sleep disorders	1.09	0.13	0.74	0.87	1.37	0.46
Previous suicidal ideation	0.00	0.00	-52.48	0.00	0.00	<0.001
<b>Overlapping medication</b>						
Benzodiazepines	1.83	0.21	5.37	1.47	2.28	<0.001
Gabapentinoids	1.10	0.23	0.44	0.73	1.65	0.66
Antipsychotics	1.13	0.38	0.37	0.59	2.18	0.71