

Supplemental Digital Content

Table S1. Generic Drug Names for Included Medication Classes	S2
Table S2. ICD-9-CM Codes for Included Diagnosis Categories	S3
Table S3. Tests of Proportional Hazards Assumption in Associations with Long-Term Opioid Receipt	S4
Table S4. Additional Sensitivity Analyses of Associations with Long-Term Opioid Receipt	S5

Table S1. Generic Drug Names for Included Medication Classes

Medication Class	Generic Drug Names (Alone or in Combinations)
Opioid	buprenorphine [<i>transdermal Butrans only</i>], butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, nalbuphine, opium alkaloids, oxycodone, oxymorphone, pentazocine, propoxyphene, tapentadol, tramadol
Opioid use disorder	buprenorphine [<i>excluding Butrans</i>], naltrexone
Alcohol use disorder	acamprosate, disulfiram
Tobacco cessation	nicotine, varenicline
Selective serotonin reuptake inhibitor	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Serotonin-norepinephrine reuptake inhibitor	desvenlafaxine, venlafaxine
Other antidepressant	amitriptyline/chlordiazepoxide, amitriptyline/perphenazine, bupropion, doxepin, fluoxetine/olanzapine, isocarboxazid, mirtazapine, nefazodone, phenelzine, tranylcypromine, trazodone, vilazodone
Benzodiazepine	alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam
Non-benzodiazepine hypnotic	eszopiclone, zaleplon, zolpidem
Attention-deficit/hyperactivity disorder	amphetamine, atomoxetine, dextmethylphenidate, dextroamphetamine, lisdexamfetamine, methamphetamine, methylphenidate
Mood stabilizer	lamotrigine, lithium
Antipsychotic	aripiprazole, asenapine, chlorpromazine, clozapine, droperidol, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, mesoridazine, molindone, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, thioridazine, trifluoperazine, ziprasidone

Table S2. ICD-9-CM Codes for Included Diagnosis Categories

Diagnosis Category	ICD-9-CM Codes
Cancer	140.x – 172.x, 174.x – 209.xx, 235.x – 239.xx, 338.3
Painful conditions	Musculoskeletal conditions: 710.x – 739.x; Other neck and back conditions: 756.10, 756.11, 756.12, 756.13, 756.19, 805.4, 805.8, 839.0x, 839.1x, 839.2x, 839.42, 846.x, 847.0, 847.1, 847.2, 847.3, 847.9; Headache/migraine: 346.xx, 307.81
Opioid use disorder	304.0x, 304.7x, 305.5x
Non-opioid substance use disorder	303.xx, 304.xx (except 304.0x, 304.7x), 305.xx (except 305.1, 305.5x)
Depressive disorder	296.2x, 296.3x, 300.4, 311
Suicide attempt or other self-injury (definite or uncertain)	E95x.x, E98x.x
Anxiety disorder	300.0x, 300.21, 300.22, 300.23, 300.3, 308.3, 309.81
Sleep disorder	307.4x, 327.xx, 347.xx, 780.5x
Motor vehicle crash	E81x.x

Table S3. Tests of Proportional Hazards Assumption in Associations with Long-Term Opioid Receipt

Prior Diagnosis	Unmodified Follow-Up Time		Modified Follow-Up Time ^a	
	Estimate at Index Date HR (95% CI)	Time Interaction b (SE)	Estimate at Index Date HR (95% CI)	Time Interaction b (SE)
ODD	14.08 (11.54-17.18)	-0.47 (0.12)	11.70 (9.36-14.64)	-0.34 (0.11)
SUD	3.11 (2.79-3.48)	-0.05 (0.03)	3.41 (3.06-3.80)	-0.01 (0.03)
Depressive disorder	2.05 (1.94-2.16)	-0.02 (0.01)	2.11 (2.00-2.23)	-0.05 (0.01)
Suicide attempt/Self-injury	2.44 (1.40-4.24)	-0.05 (0.18)	2.54 (1.46-4.40)	0.10 (0.16)
Anxiety disorder	2.10 (1.98-2.23)	-0.06 (0.02)	2.21 (2.08-2.35)	-0.08 (0.02)
Sleep disorder	1.87 (1.76-1.98)	-0.03 (0.01)	1.77 (1.67-1.88)	0.01 (0.01)
Motor vehicle crash ^b	1.78 (1.32-2.41)	-0.08 (0.09)	2.24 (1.68-2.98)	-0.16 (0.10)
Prior Medication				
ODD medication	6.23 (4.74-8.19)	-0.34 (0.14)	7.43 (5.72-9.66)	-0.26 (0.12)
AUD medication	3.67 (2.62-5.13)	-0.02 (0.09)	3.21 (2.29-4.51)	0.13 (0.07)
Tobacco cessation	1.67 (1.47-1.91)	0.05 (0.03)	1.58 (1.37-1.81)	0.08 (0.04)
SSRI	1.59 (1.51-1.67)	0.04 (0.01)	1.62 (1.54-1.70)	0.03 (0.01)
SNRI	1.79 (1.63-1.96)	0.02 (0.02)	1.77 (1.61-1.95)	-0.02 (0.02)
Other antidepressant	1.83 (1.72-1.94)	0.02 (0.01)	1.79 (1.68-1.90)	0.03 (0.01)
Benzodiazepine	2.09 (1.99-2.19)	0.00 (0.01)	2.10 (2.00-2.20)	0.02 (0.01)
Hypnotic	1.91 (1.79-2.03)	0.01 (0.01)	1.89 (1.77-2.02)	0.02 (0.01)
ADHD medication	1.53 (1.35-1.73)	0.00 (0.03)	1.58 (1.39-1.79)	0.02 (0.03)
Mood stabilizer	1.94 (1.65-2.28)	0.01 (0.04)	1.98 (1.67-2.34)	-0.02 (0.04)
Antipsychotic	2.62 (2.35-2.94)	0.00 (0.02)	2.62 (2.33-2.94)	0.00 (0.03)

Note. Adjusted Cox regressions with predictor by linear time interaction, estimated in randomly selected 10% (n = 1 031 196) of patients given memory limitations. Interaction term represents annual change in log hazard difference. Models also control sex, index age group, and calendar year of index date. HR = hazard ratio. CI = confidence interval. SE = standard error. ODD = opioid use disorder. SUD = non-opioid substance use disorder. AUD = alcohol use disorder. SSRI = selective serotonin reuptake inhibitor. SNRI = serotonin-norepinephrine reuptake inhibitor. ADHD = attention-deficit/hyperactivity disorder.

^a Censoring date set to 6 months prior to end of observed follow-up to examine influence of 6-month requirement for long-term opioids on change over time in risk (n = 825 021).

^b Motor vehicle crashes include patients aged 19 years or older at index (n = 919 669; n = 734 370 for modified follow-up time).

Table S4. Additional Sensitivity Analyses of Associations with Long-Term Opioid Receipt

Prior Diagnosis	Pain Models HR (95% CI)	Logistic Models OR (95% CI)	Youth Models HR (95% CI)	Stricter Models HR (95% CI)	Past-Year Models HR (95% CI)
ODU	7.95 (7.49-8.45)	11.62 (10.45-12.91) ^a	10.19 (8.74-11.89)	12.62 (11.75-13.57)	8.97 (8.35-9.64)
SUD	2.99 (2.90-3.07)	3.45 (3.29-3.62)	3.19 (2.94-3.47)	3.71 (3.58-3.85)	3.47 (3.35-3.60)
Depressive disorder	1.79 (1.77-1.82)	2.06 (2.02-2.11)	2.66 (2.52-2.82)	2.14 (2.10-2.18)	2.09 (2.05-2.12)
Suicide attempt/Self-injury	2.24 (1.95-2.59)	2.84 (2.20-3.67)	2.34 (1.65-3.33)	3.13 (2.58-3.79)	2.98 (2.49-3.57)
Anxiety disorder	1.77 (1.75-1.80)	2.07 (2.02-2.12)	2.96 (2.79-3.15)	2.15 (2.11-2.20)	2.19 (2.15-2.23)
Sleep disorder	1.62 (1.60-1.65)	1.86 (1.82-1.91)	3.59 (3.30-3.90)	1.89 (1.85-1.93)	1.87 (1.84-1.90)
Motor vehicle crash ^b	1.70 (1.58-1.83)	2.28 (2.02-2.57)	2.34 (1.85-2.96)	2.05 (1.85-2.27)	2.51 (2.30-2.75)
Prior Medication					
ODU medication	4.85 (4.51-5.21)	5.81 (5.10-6.61)	11.62 (9.54-14.16)	7.20 (6.59-7.88)	5.87 (5.42-6.35)
AUD medication	2.94 (2.70-3.20)	2.91 (2.50-3.39)	4.82 (2.51-9.28)	3.63 (3.24-4.07)	3.37 (3.03-3.74)
Tobacco cessation	1.71 (1.65-1.77)	1.68 (1.60-1.78)	4.98 (3.95-6.29)	1.94 (1.85-2.03)	1.92 (1.84-2.00)
SSRI	1.59 (1.57-1.61)	1.68 (1.64-1.71)	2.72 (2.58-2.87)	1.76 (1.73-1.79)	1.78 (1.76-1.80)
SNRI	1.66 (1.63-1.70)	1.88 (1.81-1.95)	3.41 (3.00-3.87)	1.87 (1.81-1.93)	1.89 (1.84-1.94)
Other antidepressant	1.76 (1.73-1.78)	1.84 (1.79-1.89)	3.15 (2.92-3.40)	1.99 (1.95-2.03)	2.02 (1.98-2.05)
Benzodiazepine	1.90 (1.88-1.92)	2.04 (2.00-2.08)	4.49 (4.22-4.78)	2.16 (2.13-2.20)	2.39 (2.36-2.42)
Hypnotic	1.82 (1.79-1.84)	2.00 (1.94-2.05)	5.05 (4.59-5.55)	2.04 (2.00-2.09)	2.23 (2.19-2.26)
ADHD medication	1.41 (1.37-1.46)	1.56 (1.48-1.65)	1.24 (1.15-1.33)	1.57 (1.50-1.64)	1.60 (1.55-1.66)
Mood stabilizer	1.87 (1.80-1.95)	2.03 (1.90-2.18)	2.60 (2.27-2.99)	2.24 (2.12-2.37)	2.01 (1.93-2.11)
Antipsychotic	2.55 (2.47-2.62)	2.86 (2.73-3.00)	2.66 (2.41-2.94)	3.07 (2.96-3.19)	2.90 (2.82-3.00)
Analytic n	7 611 536	4 210 104	2 263 174	10 311 961	10 311 961

Note. Pain models include patients with painful conditions. Logistic models predict receipt within 1.5 years of index date (patients with at least 2 follow-up years). Youth models include patients aged 14-25 at index. Stricter models define long-term opioids as at least 183 days supply within 6 months. Past-year models include predictors from 12 months prior to index month. All models control sex, index calendar year, and (except youth models) index age group. HR = hazard ratio. OR = odds ratio. CI = confidence interval. OUD = opioid use disorder. SUD = non-opioid substance use disorder. AUD = alcohol use disorder. SSRI = selective serotonin reuptake inhibitor. SNRI = serotonin-norepinephrine reuptake inhibitor. ADHD = attention-deficit/hyperactivity disorder.

^a Estimated with option RIDGING=NONE because of ridging problem. ^b Motor vehicle crashes include patients aged 19 or older at index (n = 9 196 693; n = 6 872 690 for pain model; n = 3 733 261 for logistic model; n = 1 147 906 for youth model).