

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. International Classification of Diseases, Ninth Revision (ICD-9) Codes

Diagnosis	ICD-9 Codes
Attention-deficit/hyperactivity disorder	314.xx
Anxiety disorder	300.0x, 300.21, 300.22, 300.23, 300.3, 308.3, 309.81
Bipolar and other mood disorder	296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7, 296.8x, 296.9x
Cancer	140.x-172.x, 174.x-209.xx, 235.x-239.xx, 338.3
Depressive disorder	296.2x, 296.3x, 300.4, 311
Non-opioid substance use disorder	291.xx, 292.xx, 303.xx, 304.1x-304.6x, 304.8x-304.9x, 305.0x, 305.2x-305.4x, 305.6x-305.9x
Opioid use disorder	304.0x, 304.7x, 305.5x
Painful condition	Musculoskeletal: 710.x-739.x Other neck/back: 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: 307.81, 346.xx
Schizophrenia spectrum disorder	295.xx, 297.x, 298.x
Sleep disorder	307.4x, 327.xx, 347.xx, 780.5x
Suicide attempt or other self-injury (definite or uncertain)	E95x.x, E98x.x

eTable 2. Generic Drug Names

Medication Class	Generic Name (Alone or in Combination)
Attention-deficit/hyperactivity disorder medication	amphetamine, atomoxetine, dexamethylphenidate, dextroamphetamine, lisdexamfetamine, methamphetamine, methylphenidate
Antipsychotic	aripiprazole, asenapine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, molindone, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, ziprasidone
Benzodiazepine	alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, triazolam
Mood stabilizer	lamotrigine, lithium
Non-benzodiazepine hypnotic	eszopiclone, zaleplon, zolpidem
Opioid	buprenorphine (transdermal Butrans only), butorphanol, codeine, dihydrocodeine, fentanyl LA, fentanyl SA, hydrocodone LA, hydrocodone SA, hydromorphone LA, hydromorphone SA, levorphanol, meperidine, methadone, morphine LA, morphine SA, opium, oxycodone LA, oxycodone SA, oxymorphone LA, oxymorphone SA, pentazocine, propoxyphene, tapentadol LA, tapentadol SA, tramadol LA, tramadol SA
Opioid use disorder medication	buprenorphine (excluding Butrans, Buprenex), naltrexone
Serotonin-norepinephrine reuptake inhibitor	desvenlafaxine, levomilnacipran, venlafaxine
Selective serotonin reuptake inhibitor	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline

Abbreviations: LA, long acting opioid; SA, short acting opioid

eTable 3. Prior Mental Health Prevalence for Long-term Follow-up Sample

Prior Mental Health Factor	<i>n</i>	%
Anxiety		
Anxiety disorder	50 739	5.1%
Benzodiazepine	22 572	2.3%
Mood		
Bipolar/other mood disorder	23 387	2.3%
Depressive disorder	72 493	7.2%
Suicide attempt or self-injury	2306	0.2%
Mood stabilizer	8671	0.9%
SNRI	5008	0.5%
SSRI	67 727	6.8%
Neurodevelopment		
ADHD	78 221	7.8%
ADHD medication	91 255	9.1%
Psychosis		
Schizophrenia spectrum disorder	4386	0.4%
Antipsychotic	20 553	2.1%
Sleep		
Sleep disorder	16 760	1.7%
Non-benzodiazepine hypnotic	4854	0.5%
Substance use		
Non-opioid SUD	20 125	2.0%
OUD	1087	0.1%
OUD medication	347	0.03%
Psychotherapy		
For any diagnosis	112 373	11.2%

Included *N* = 1 000 453. ADHD, attention-deficit/hyperactivity disorder. OUD, opioid use disorder. SNRI, serotonin-norepinephrine reuptake inhibitor. SSRI, selective serotonin reuptake inhibitor. SUD, substance use disorder.

eTable 4. Prior Mental Health Conditions and Treatments Among Adolescents With and Without Prior Opioid Use Disorder

Prior Mental Health Factor	Without Prior OUD (n = 999 366)		With Prior OUD (n = 1087)	
	n	% (95% CI)	n	% (95% CI)
Anxiety				
Anxiety disorder	50 343	5.0% (5.0%-5.1%)	396	36.4% (33.6%-39.3%)
Benzodiazepine	22 399	2.2% (2.2%-2.3%)	173	15.9% (13.7%-18.1%)
Mood				
Bipolar/other mood disorder	22 971	2.3% (2.3%-2.3%)	416	38.3% (35.4%-41.2%)
Depressive disorder	71 830	7.2% (7.1%-7.2%)	663	61.0% (58.1%-63.9%)
Suicide attempt or self-injury	2251	0.2% (0.2%-0.2%)	55	5.1% (3.8%-6.4%)
Mood stabilizer	8530	0.9% (0.8%-0.9%)	141	13.0% (11.0%-15.0%)
SNRI	4944	0.5% (0.5%-0.5%)	64	5.9% (4.5%-7.3%)
SSRI	67 155	6.7% (6.7%-6.8%)	572	52.6% (49.7%-55.6%)
Neurodevelopment				
ADHD	77 838	7.8% (7.7%-7.8%)	383	35.2% (32.4%-38.1%)
ADHD medication	90 871	9.1% (9.0%-9.2%)	384	35.3% (32.5%-38.2%)
Psychosis				
Schizophrenia spectrum disorder	4285	0.4% (0.4%-0.4%)	101	9.3% (7.6%-11.0%)
Antipsychotic	20 180	2.0% (2.0%-2.1%)	373	34.3% (31.5%-37.1%)
Sleep				
Sleep disorder	16 657	1.7% (1.6%-1.7%)	103	9.5% (7.7%-11.2%)
Non-benzodiazepine hypnotic	4784	0.5% (0.5%-0.5%)	70	6.4% (5.0%-7.9%)
Substance use				
Non-opioid SUD	19 298	1.9% (1.9%-2.0%)	827	76.1% (73.5%-78.6%)
OUD medication	241	0.0% (0.0%-0.0%)	106	9.8% (8.0%-11.5%)
Psychotherapy				
For any diagnosis	111 595	11.2% (11.1%-11.2%)	778	71.6% (68.9%-74.3%)

Included N = 1 000 453. ADHD, attention-deficit/hyperactivity disorder. OUD, opioid use disorder. SNRI, serotonin-norepinephrine reuptake inhibitor. SSRI, selective serotonin reuptake inhibitor. SUD, substance use disorder.

eTable 5. Opioid Analgesic and Opioid Use Disorder Medication Receipt in Follow-up Among Adolescents With and Without Prior Opioid Use Disorder

Medication in Follow-up	Without Prior OUD (<i>n</i> = 999 366)		With Prior OUD (<i>n</i> = 1087)	
	<i>n</i>	% (95% CI)	<i>n</i>	% (95% CI)
Opioid				
Hydrocodone	739 503	74.0% (73.9%-74.1%)	789	72.6% (69.9%-75.2%)
Oxycodone	227 701	22.8% (22.7%-22.9%)	299	27.5% (24.9%-30.2%)
Codeine	198 309	19.8% (19.8%-19.9%)	214	19.7% (17.3%-22.1%)
Tramadol	78 429	7.9% (7.8%-7.9%)	223	20.5% (18.1%-22.9%)
Propoxyphene	61 828	6.2% (6.1%-6.2%)	68	6.3% (4.8%-7.7%)
Meperidine	7958	0.8% (0.8%-0.8%)	11	1.0% (0.4%-1.6%)
Hydromorphone	4258	0.4% (0.4%-0.4%)	10	0.9% (0.4%-1.5%)
Morphine	1553	0.2% (0.2%-0.2%)	7	0.6% (0.2%-1.1%)
Tapentadol	1025	0.1% (0.1%-0.1%)	4	0.4% (0.0%-0.7%)
Fentanyl	588	0.1% (0.1%-0.1%)	3	0.3% (0.0%-0.6%)
Methadone	389	0.0% (0.0%-0.0%)	10	0.9% (0.4%-1.5%)
Other opioids	1827	0.2% (0.2%-0.2%)	5	0.5% (0.1%-0.9%)
OUD medication				
Any medication	3435	0.3% (0.3%-0.4%)	168	15.5% (13.3%-17.6%)

Included *N* = 1 000 453. Adolescents without prior OUD had a median of 823 follow-up days (interquartile range [IQR], 440-1436), whereas those with prior OUD had a median of 672 follow-up days (IQR, 378-1113). OUD, opioid use disorder.

eTable 6. Pain Condition Cohort and Test of Proportional Hazards

Prior Mental Health Factor	Pain Cohort Model ^a	Proportional Hazards Test Model ^b	
	HR (95% CI)	HR at Index (95% CI)	Time Interaction <i>b</i> (SE)
Anxiety disorder			
Anxiety disorder	2.25 (1.89-2.69)	3.11 (2.63-3.68)	-0.07 (0.03)
Benzodiazepine	3.65 (3.03-4.39)	5.27 (4.37-6.36)	-0.15 (0.04)
Mood			
Bipolar/other mood disorder	3.01 (2.43-3.73)	3.59 (2.90-4.45)	-0.04 (0.04)
Depressive disorder	2.47 (2.14-2.86)	3.18 (2.77-3.66)	-0.03 (0.02)
Suicide attempt or self-injury	2.59 (1.23-5.44)	2.22 (0.99-4.97)	0.20 (0.13)
Mood stabilizer	2.73 (1.94-3.84)	3.51 (2.50-4.92)	-0.07 (0.06)
SNRI	3.26 (2.25-4.72)	3.88 (2.68-5.62)	0.00 (0.06)
SSRI	2.61 (2.25-3.02)	3.23 (2.80-3.72)	-0.04 (0.02)
Neurodevelopment			
ADHD	1.64 (1.38-1.94)	1.73 (1.46-2.05)	0.00 (0.03)
ADHD medication	1.59 (1.35-1.86)	1.62 (1.38-1.90)	0.03 (0.03)
Psychosis			
Schizophrenia spectrum disorder	2.35 (1.36-4.06)	2.50 (1.47-4.26)	0.08 (0.08)
Antipsychotic	3.37 (2.71-4.18)	3.87 (3.12-4.81)	-0.04 (0.04)
Sleep			
Sleep disorder	3.62 (2.90-4.51)	4.57 (3.62-5.78)	-0.14 (0.05)
Non-benzodiazepine hypnotic	6.33 (4.84-8.26)	8.90 (6.71-11.81)	-0.18 (0.06)
Substance use			
Non-opioid SUD	3.49 (2.82-4.34)	4.44 (3.62-5.45)	-0.05 (0.04)
OUD	4.85 (2.31-10.21)	13.93 (8.23-23.57)	-0.32 (0.16)
OUD medication	2.23 (0.31-15.83)	25.05 (10.96-57.21)	-1.83 (1.04)
Psychotherapy			
For any diagnosis	2.03 (1.78-2.32)	2.16 (1.89-2.47)	-0.01 (0.02)
Adolescents (n)	229 913	1 000 453	
Long-term opioid therapy (n)	1286	2846	

All models adjusted for sex, index age, and index calendar year. ADHD, attention-deficit/hyperactivity disorder. HR, hazard ratio. OUD, opioid use disorder. SNRI, serotonin-norepinephrine reuptake inhibitor. SSRI, selective serotonin reuptake inhibitor. SUD, substance use disorder.

^a Restricted to adolescents with past-90-day painful condition diagnoses.

^b Included a linear follow-up time (in years) × mental health interaction.

eTable 7. Additional Sensitivity Analyses

Prior Mental Health Factor	Stricter Model ^a	Past-Year Model ^b	2010 Model ^c
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Anxiety			
Anxiety disorder	2.75 (2.26-3.36)	3.06 (2.67-3.50)	2.95 (2.11-4.14)
Benzodiazepine	3.79 (3.02-4.75)	4.47 (3.84-5.19)	5.26 (3.66-7.54)
Mood			
Bipolar/other mood disorder	3.25 (2.51-4.20)	3.17 (2.64-3.81)	4.38 (2.94-6.51)
Depressive disorder	3.37 (2.89-3.93)	3.00 (2.68-3.35)	3.99 (3.02-5.27)
Suicide attempt or self-injury	4.29 (1.78-10.34)	3.10 (1.39-6.91)	3.37 (0.84-13.54)
Mood stabilizer	3.26 (2.22-4.78)	3.04 (2.34-3.96)	4.26 (2.33-7.80)
SNRI	3.99 (2.70-5.90)	3.77 (2.80-5.09)	5.54 (2.46-12.46)
SSRI	2.86 (2.43-3.37)	2.99 (2.69-3.34)	4.30 (3.26-5.69)
Neurodevelopment			
ADHD	1.77 (1.46-2.14)	1.62 (1.40-1.87)	1.61 (1.11-2.31)
ADHD medication	1.71 (1.43-2.04)	1.68 (1.49-1.90)	1.41 (0.98-2.02)
Psychosis			
Schizophrenia spectrum disorder	2.51 (1.30-4.85)	3.58 (2.30-5.55)	3.00 (1.12-8.06)
Antipsychotic	4.04 (3.19-5.13)	3.54 (2.96-4.22)	3.72 (2.38-5.80)
Sleep			
Sleep disorder	3.81 (2.89-5.03)	3.95 (3.20-4.86)	4.57 (2.93-7.13)
Non-benzodiazepine hypnotic	6.11 (4.38-8.53)	7.12 (5.65-8.97)	10.10 (5.99-17.04)
Substance use			
Non-opioid SUD	3.96 (3.12-5.04)	4.07 (3.40-4.87)	4.88 (3.23-7.39)
ODU	9.25 (4.61-18.58)	10.69 (6.80-16.79)	8.73 (2.80-27.23)
ODU medication	10.59 (3.41-32.90)	12.39 (5.90-26.03)	-- ^d
Psychotherapy			
For any diagnosis	2.05 (1.76-2.38)	2.12 (1.90-2.36)	2.62 (2.00-3.43)
Adolescents (n)	1 000 453	1 000 453	107 212
Long-term opioid therapy (n)	1062	2846	278

All models adjusted for sex, index age, and (except 2010 model) index calendar year. ADHD, attention-deficit/hyperactivity disorder. HR, hazard ratio. OUD, opioid use disorder. SNRI, serotonin-norepinephrine reuptake inhibitor. SSRI, selective serotonin reuptake inhibitor. SUD, substance use disorder.

^a Cox proportional hazards regression predicting stricter long-term definition (opioid supply every day within a 6-month window).

^b Cox proportional hazards regression predicting long-term opioids from mental health in the year prior to first opioid receipt.

^c Cox proportional hazards regression predicting long-term opioids among adolescents with first opioid receipt in 2010.

^d Hazard ratio could not be estimated with meaningful precision because of insufficient power.