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FIGURE S1. Study design

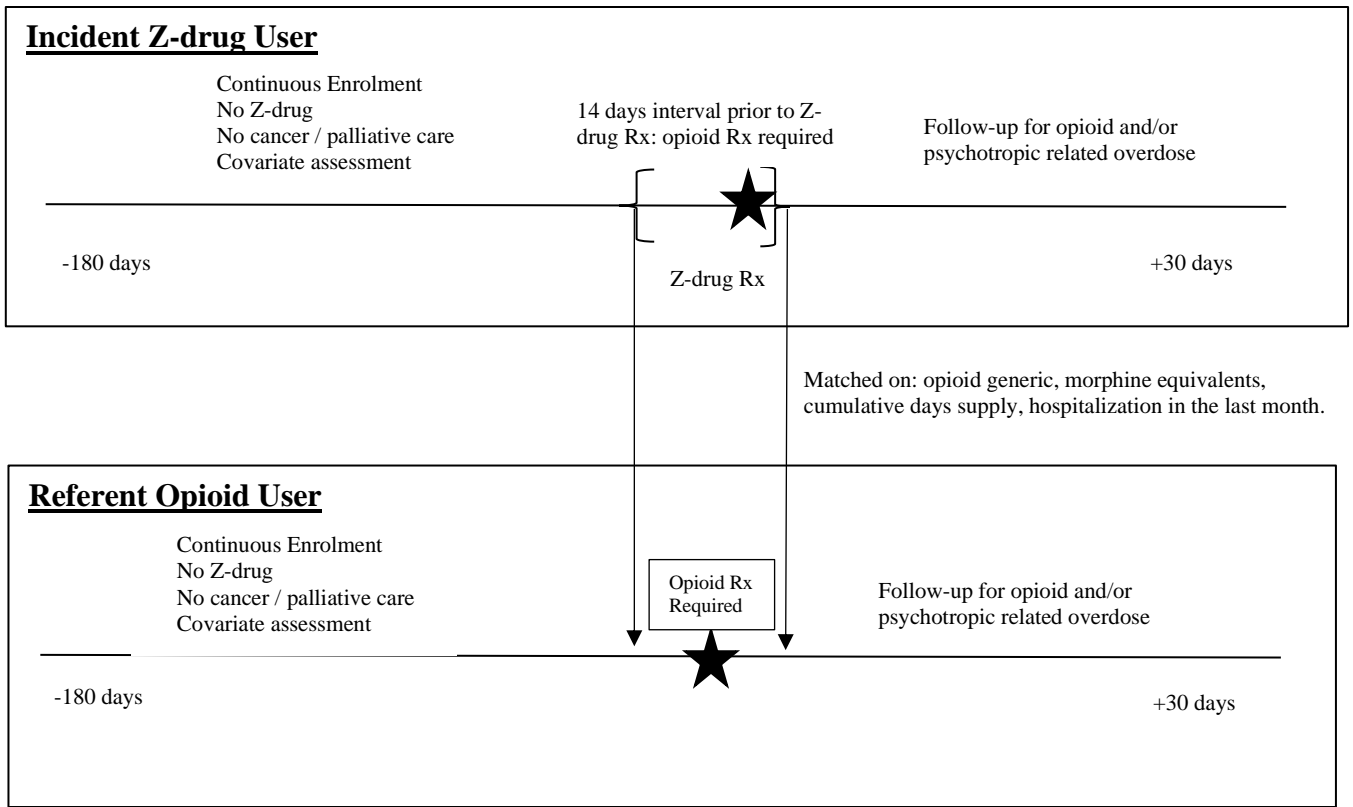


TABLE S1. Included and excluded opioid formulations

Included Formulations	Excluded Formulations
Patch, tablet, tablet extended release 12 and 24 hs, tablet rapid dissolution, tablet sublingual, tablet SR 12hs, tablet eff, tablet hyp, tablet sa, tablet sol, capsule, capsule extended release.	Ampul, syringe, film, vial, spray, elixir, liquid, powder, oral suspension, solution, suspension er 12hs, syrup, disposable syringe, oral concentration, cartridge, CPMP 24hs, CPBP 17-83, CPBP 25-75 and TBMP 24 hs.

TABLE S2. ICD-9 and ICD-10 codes used in primary outcome and sensitivity analyses

Outcome	Overdose group	ICD-9 Code	ICD-10 Code
Primary Outcome	Opioid-related overdose	965.00, 965.02, 965.09, E850.0, E850.1, E850.2	T40.0X1, T40.0X3, T40.0X4, T40.2X1, T40.2X3, T40.2X4, T40.3X1, T40.3X3, T40.3X4, T40.4X1, T40.4X3, T40.4X4
	Psychotropic-related overdose	967.*, 969.*	T423X1A, T423X3A, T423X4A, T424X1A, T424X3A, T424X4A, T426X1A, T426X3A, T426X4A, T4271XA, T4273XA, T4274XA, T43011A, T43013A, T43014A, T43021A, T43023A, T43024A, T431X1A, T431X3A, T431X4A, T43201A, T43203A, T43204A, T43211A, T43213A, T43214A, T43221A, T43223A, T43224A, T43291A, T43293A, T43294A, T433X1A, T433X3A, T433X4A, T434X1A, T434X3A, T434X4A, T43501A, T43503A, T43504A, T43591A, T43593A, T43594A, T438X1A, T438X3A, T438X4A, T4391XA, T4393XA, T4394XA
	Intentional self-harm (exclusion)	E950.xx, E951.xx, E952.xx, E953.xx, E954.xx, E955.xx, E956.xx, E957.xx, E958.xx, E959.xx, E980.xx, E981.xx, E982.xx, E983.xx, E984.xx, E985.xx, E986.xx, E987.xx, E988.xx, E989.xx, V62.84	T40.0X2, T40.2X2, T40.3X2, T40.4X2, T423X2A, T424X2A, T426X2A, T4272XA, T43012A, T43022A, T431X2A, T43202A, T43212A, T43222A, T43292A, T433X2A, T434X2A, T43502A, T43592A, T438X2A, T4392XA
Sensitivity Analysis	Respiratory Failure Codes	518.81, 518.82, 786.03, 786.05, 786.09, 799.0*, 799.1*	J9600, J9601, J9602, J9690, J9691, J9692, R0602, R0603, R0681, R0683, R0689, R0901, R0902, R092
Sensitivity Analysis	Sedative/Hypnotic Overdose (exclusion)	967.8	T426X1A, T426X3A, T426X4A, T4271XA, T4273XA, T4274XA

TABLE S3. Complete unadjusted and propensity-score weighted baseline characteristics of Z-drug exposed and unexposed opioid users

Characteristic	Unadjusted			Accounting for Propensity Score Strata		
	Z-drugs plus Opioids	Opioids alone	Std Diff ¹	Z-drugs plus Opioids	Opioids alone	Std Diff ¹
Number of Individuals	510,529	510,529		510,527	510,529	
Age - years, mean (SD)	49.8 (14.4)	46.9 (16.5)	0.19	49.8 (14.4)	50.7 (15.8)	-0.06
Male sex – n(%)	196,075 (38.4)	220,692 (43.2)	-0.10	196,075 (38.4)	192,106 (37.6)	0.01
Charlson score - median (IQR)	0.5 (1.0)	0.4 (0.9)	0.07	0.5 (1.0)	0.5 (1.0)	-0.02
<i>Opioid Related Variables</i>						
Opioid prescribed**						
Buprenorphine - n (%)	1424 (0.3)	1424 (0.3)	0.00	1424 (0.3)	1309 (0.3)	0.00
Codeine - n (%)	23,592 (4.6)	23,592 (4.6)	0.00	23,592 (4.6)	21,859 (4.3)	0.02
Fentanyl - n (%)	779 (0.2)	779 (0.2)	0.00	779 (0.2)	1041 (0.2)	-0.01
Hydrocodone - n (%)	283,301 (55.5)	283,301 (55.5)	0.00	283,299 (55.5)	282,124 (55.3)	0.00
Meperidine - n (%)	5,026 (1.0)	5,026 (1.0)	0.00	5,026 (1)	4,800 (0.9)	0.00
Methadone - n (%)	383 (0.1)	383 (0.1)	0.00	383 (0.1)	439 (0.1)	0.00
Morphine - n (%)	683 (0.1)	683 (0.1)	0.00	683 (0.1)	850 (0.2)	0.01
Oxycodone - n (%)	100,241 (19.6)	100,241 (19.6)	0.00	100,241 (19.6)	97,394 (19.1)	0.01
Tramadol - n (%)	64,229 (12.6)	64,229 (12.6)	0.00	64,229 (12.6)	66,631 (13.1)	-0.01
Days' supply for last prescription – mean (SD)	11.5 (11.9)	11.2 (11.9)	0.02	11.5 (11.9)	11.8 (11.8)	-0.03
Cumulative supply days in the last 180 – mean (SD)**	35.7 (51.5)	35.1 (51.8)	0.01	35.7 (51.5)	40.8 (54.9)	-0.09

Characteristic	Unadjusted			Accounting for Propensity Score Strata		
	Z-drugs plus Opioids	Opioids alone	Std Diff ¹	Z-drugs plus Opioids	Opioids alone	Std Diff ¹
MEQ from the last supply – mean (SD)**	486.8 (2360.0)	482.2 (2360.5)	0.00	486.8 (2359.9)	498.8 (2087.7)	0.00
Cumulative MEQ in the last 180 days – mean (SD)**	1475.9 (7342.7)	1464.9 (7344.3)	0.00	1475.9 (7342.7)	1650.8 (7214.5)	-0.02
Baseline opioid dependence - n (%)	2853 (0.6)	2240 (0.4)	0.03	2853 (0.6)	3050 (0.6)	0.00
Baseline opioid abuse - n (%)	303 (0.1)	223 (0.0)	0.05	303 (0.1)	319 (0.1)	0.00
<i>Comorbidities</i>						
Hypertension - n (%)	147,045 (28.8)	129,967 (25.5)	0.07	147,045 (28.8)	152,981 (30.0)	-0.02
COPD - n (%)	19,966 (3.9)	16,574 (3.2)	0.04	19,966 (3.9)	21,522 (4.2)	-0.01
Heart failure - n (%)	13,596 (2.7)	9,634 (1.9)	0.05	13,595 (2.7)	14,406 (2.8)	0.00
Dementia - n (%)	4,499 (0.9)	3,631 (0.7)	0.02	4499 (0.9)	4871 (1.0)	0.00
Stroke - n (%)	6,805 (1.3)	4,653 (0.9)	0.04	6805 (1.3)	7234 (1.4)	0.00
Epilepsy or convulsions - n (%)	5,317 (1.0)	4,263 (0.8)	0.02	5317 (1.0)	5485 (1.1)	0.00
Diabetes - n (%)	58,606 (11.5)	56,285 (11.0)	0.02	58,606 (11.5)	61,628 (12.0)	-0.02
Smoking - n (%)	29,361 (5.8)	29,274 (5.7)	0.00	29,360 (5.8)	30,084 (5.9)	0.00
Obesity - n (%)	29,784 (5.8)	28,912 (5.7)	0.01	29,783 (5.8)	30,294 (5.9)	0.00
Renal failure - n (%)	22,180 (4.3)	19,286 (3.8)	0.03	21,012 (4.4)	21,771 (4.6)	-0.00
Chronic Liver Disease - n (%)	6,709 (1.3)	5,530 (1.1)	0.02	6,248 (1.3)	6,418 (1.3)	0.00
Asthma - n (%)	25,400 (5.0)	21,531 (4.4)	0.02	23,195 (4.9)	23,817 (5.0)	-0.01
Ischemic Heart Disease - n (%)	38,782 (7.6)	30,637 (6.0)	0.06	36,539 (7.7)	38,382 (8.1)	-0.01
Parkinson Disease - n (%)	1,231 (0.2)	1,099 (0.2)	0.00	1,189 (0.2)	1,298 (0.3)	0.00

Characteristic	Unadjusted			Accounting for Propensity Score Strata		
	Z-drugs plus Opioids	Opioids alone	Std Diff ¹	Z-drugs plus Opioids	Opioids alone	Std Diff ¹
Allergic Rhinitis - n (%)	34,432 (6.7)	27,489 (5.4)	0.05	31,826 (6.7)	31,200 (6.6)	0.00
Pancreatitis - n (%)	3,051 (0.6)	2,295 (0.4)	0.03	2,938 (0.6)	2,601 (0.5)	0.01
Urinary Incontinence - n (%)	5,430 (1.1)	4,350 (0.9)	0.02	4,828 (1.0)	5,106 (1.1)	-0.01
<i>Pain Related Conditions</i>						
Neuropathic pain - n (%)	71,159 (13.9)	65,147 (12.8)	0.03	59,447 (12.5)	61,915 (13.0)	-0.01
Back pain - n (%)	140,896 (27.6)	131,853 (25.8)	0.04	123,748 (26.0)	126,048 (26.5)	-0.01
Neck pain - n (%)	64,764 (12.7)	53,020 (10.4)	0.07	59,713 (12.5)	61,742 (13.0)	-0.01
Joint pain - n (%)	160,666 (31.5)	136,697 (26.8)	0.10	159,419 (33.5)	165,367 (34.7)	-0.02
Tendon/Bursal pain - n (%)	61,081 (12.0)	45,806 (9.0)	0.10	59,447 (12.5)	61,915 (13.0)	-0.01
Musculoskeletal injury (severe) - n (%)	39,804 (7.8)	31,594 (6.2)	0.06	36,157 (7.6)	38,081 (8.0)	-0.01
Urinary calculus - n (%)	23,719 (4.6)	25,393 (5.0)	-0.02	11,448 (2.2)	10,606 (2.2)	0.01
Dental pain - n (%)	2,324 (0.5)	5,882 (1.2)	-0.08	2194 (0.5)	2108 (0.4)	0.00
Pain not elsewhere specified - n (%)	36,132 (7.1)	29,382 (5.8)	0.05	29,815 (6.3)	30,855 (6.5)	-0.01
Generalized pain - n (%)	2,815 (0.6)	2,331 (0.5)	0.01	2192 (0.5)	2261 (0.5)	0.00
Pain related to psychological factors - n (%)	856 (0.2)	524 (0.1)	0.03	533 (0.1)	565 (0.1)	0.00
Fibromyalgia - n (%)	26,049 (5.1)	18,383 (3.6)	0.07	23,491 (4.9)	24,630 (5.2)	-0.01
Migraine - n (%)	54,859 (10.7)	37,570 (7.4)	0.12	51,936 (10.9)	52,189 (11.0)	0.00
Open wound lesion - n (%)	7,588 (1.5)	7,843 (1.5)	0.00	7,395 (1.6)	7,820 (1.6)	0.00
Rheumatoid Arthritis - n (%)	7,821 (1.5)	6,858 (1.3)	0.02	7,475 (1.6)	7,886 (1.7)	0.00
<i>Psychiatric Related Conditions</i>						

Characteristic	Unadjusted			Accounting for Propensity Score Strata		
	Z-drugs plus Opioids	Opioids alone	Std Diff ¹	Z-drugs plus Opioids	Opioids alone	Std Diff ¹
Unspecified mental disorder - n (%)	2,550 (0.5)	1,469 (0.3)	0.03	2,436 (0.5)	2,485 (0.5)	0.00
Depression diagnosis - n (%)	63,820 (12.5)	39,366 (7.7)	0.16	58,107 (12.2)	59,550 (12.5)	0.00
ADHD - n (%)	7,726 (1.5)	6,256 (1.2)	0.03	6,539 (1.4)	6,669 (1.4)	0.00
Bipolar Disorder - n (%)	8,299 (1.6)	4,601 (0.9)	0.06	8,175 (1.7)	8,403 (1.8)	0.00
Anxiety Disorder - n (%)	47,594 (9.3)	30,780 (6.0)	0.12	40,932 (8.6)	42,330 (8.9)	-0.01
Insomnia diagnosis - n (%)	56,978 (11.2)	7,939 (1.6)	0.40	48,143 (10.1)	41,912 (8.8)	0.04
Schizophrenia diagnosis - n (%)	2,397 (0.5)	1,532 (0.3)	0.03	2,298 (0.5)	2,266 (0.5)	0.00
Personality disorder - n (%)	1,322 (0.3)	795 (0.2)	0.02	817 (0.2)	867 (0.2)	0.00
Drug abuse dependence - n (%)	4,549 (0.9)	3,605 (0.7)	0.02	4,393 (0.9)	4,513 (0.9)	0.00
Alcohol abuse or dependence - n (%)	5,716 (1.1)	4,377 (0.9)	0.02	5,405 (1.1)	5,565 (1.2)	0.00
Sedative abuse or dependence - n (%)	345 (0.1)	194 (0.0)	0.04	268 (0.1)	282 (0.1)	0.00
Past suicide attempt - n (%)	1277 (0.3)	592 (0.1)	0.04	1,132 (0.2)	1,116 (0.2)	0.00
<i>Psychotropic Concomitant Medication</i>						
Benzodiazepine use - n (%)	140,489 (27.5)	84,715 (16.6)	0.27	130,406 (27.4)	134,112 (28.2)	-0.02
Benzodiazepine equivalent dose – mean (SD)	50.8 (1061.6)	33.0 (577.0)	0.02	47.1 (355.1)	67.8 (1954.5)	-0.01
Antidepressants (SSRI) – n (%)	166,879 (32.7)	108,192 (21.2)	0.26	154,796 (32.5)	160,144 (33.7)	-0.02
Lithium - n (%)	1,810 (0.4)	1,040 (0.2)	0.04	1,651 (0.3)	1,723 (0.4)	0.00
Antipsychotics - n (%)	14,818 (2.9)	8,511 (1.7)	0.08	13,556 (2.8)	14,268 (3.0)	-0.01
Muscle relaxants - n (%)	109,471 (21.4)	91,956 (18.0)	0.09	101,120 (21.2)	102,902 (21.6)	-0.01
Gabapentinoids - n (%)	44,854 (8.8)	33,470 (6.6)	0.08	39,918 (8.4)	42,210 (8.9)	-0.02

Characteristic	Unadjusted			Accounting for Propensity Score Strata		
	Z-drugs plus Opioids	Opioids alone	Std Diff ¹	Z-drugs plus Opioids	Opioids alone	Std Diff ¹
<i>Healthcare use Measures</i>						
No. Hospitalizations in the past year – mean (SD)	0.3 (0.6)	0.2 (0.5)	0.05	0.3 (0.6)	0.3 (0.6)	0.00
No. Physician visits in the past year - median (IQR)	5.0 (4.0-7.0)	4.2 (3.0-6.0)	0.19	5.0 (4.0-7.0)	5.1 (3.7-6.9)	-0.03
No. Psychiatric visits - mean (SD)	0.3 (0.9)	0.2 (0.7)	0.12	0.3 (0.9)	0.3 (0.9)	0.00
No. Psychiatric hospitalizations – mean (SD)	0.0 (0.1)	0.0 (0.1)	0.04	0.0 (0.1)	0.0 (0.1)	0.00
No. ED visits – mean (SD)	0.4 (1.2)	0.4 (1.0)	0.01	0.4 (1.2)	0.4 (1.0)	0.00
No. ICD diagnoses (3rd digit level) – median (IQR) [^]	9.7 (8.0-13.0)	8.0 (7.0-11.0)	0.20	9.7 (8.0-13.0)	9.6 (8.0-13.0)	-0.04
Total No. medications% – median (IQR)	6.8 (6.0-9.0)	5.3 (4.0-7.0)	0.32	6.7 (6.0-9.0)	6.9 (6.0-9.0)	-0.04
Hospitalized past month - n (%)**	77,365 (15.2)	77,365 (15.2)	0.00	73,475 (15.4)	74,418 (15.6)	0.00

SSRI: selective serotonin reuptake inhibitors; COPD: chronic obstructive pulmonary disease; SD: standard deviation; IQR: interquartile range; MEQ: Morphine Equivalents; ADHD: Attention Deficit and Hyperactivity Disorder; No.: Number of; ED: Emergency Department; ICD9: International Classification of Diseases 9th Edition.

% Other than opioids and/or z-drugs; [^] Not including insomnia; ** Variables used in the matching process.

Std Diff estimated as $\sqrt{\frac{\bar{x}_{exp} - \bar{x}_{ref}}{s_{exp}^2 + s_{ref}^2}}$ where s² represents the sample variance in both exposed and unexposed groups

TABLE S4. Absolute survival differences during 30-days follow-up.

Day	Daily Survival Probabilities Z-drugs users plus Opioids	Daily Survival Probabilities opioids alone users	Survival difference
1	1	1	-0.000020773
2	1	1	-0.000039016
3	1	1	-0.00005509
4	0.9999	1	-0.000069314
5	0.9999	1	-0.000081967
6	0.9999	1	-0.000093286
7	0.9999	0.9999	-0.000103474
8	0.9998	0.9999	-0.000112704
9	0.9998	0.9999	-0.000121122
10	0.9998	0.9999	-0.00012885
11	0.9998	0.9999	-0.000135995
12	0.9998	0.9999	-0.000142644
13	0.9998	0.9999	-0.000148875
14	0.9998	0.9999	-0.00015475
15	0.9997	0.9999	-0.000160326
16	0.9997	0.9999	-0.000165647
17	0.9997	0.9999	-0.000170753
18	0.9997	0.9999	-0.000175674
19	0.9997	0.9999	-0.000180434
20	0.9997	0.9999	-0.000185048
21	0.9997	0.9999	-0.000193852
22	0.9997	0.9999	-0.000198016
23	0.9997	0.9999	-0.000201974
24	0.9996	0.9999	-0.000205657
25	0.9996	0.9999	-0.000208957
26	0.9996	0.9999	-0.000211707
27	0.9996	0.9999	-0.000213659
28	0.9996	0.9999	-0.000214442
29	0.9996	0.9999	-0.000213505
30	0.9996	0.9998	-0.000250033

TABLE S5. Sensitivity analyses varying the primary outcome definition.

Definition	Hazard Ratio [HR]	95% Confidence Interval [CI]
Requiring a respiratory failure code	1.70	0.96 - 3.03
Removing overdose due to sedative/hypnotics	1.49	1.13 - 1.96
Requiring only an opioid overdose criterion	1.38	0.95 - 2.08

TABLE S6. Sensitivity analysis restricting to patients without mental health conditions.

Level of Adjustment	Exposed to Z-drugs plus opioids		Exposed to opioids alone		HR (95% CI)
	Events	Person-years	Events	Person-years	
30-day Intention-to-treat Opioid and/or psychotropic overdose (primary outcome)					
Unadjusted	74	28,700	22	27,598	3.26 (2.02 – 5.24)
Fine PS stratification	74	28,700	22	27,598	1.95 (1.31 – 2.89)
<p>Conditions excluded in the present analysis</p> <ul style="list-style-type: none"> • Any diagnosis of schizophrenia • Any diagnosis of Bipolar Disorder • Any diagnosis of anxiety • Any diagnosis of depression • Any diagnosis of unspecified mental health disorder • Any diagnosis of personality disorder • Any diagnosis of drug abuse/dependence • Any diagnosis of alcohol abuse/dependence • Any code for suicide attempt • Any diagnosis for ADHD <p><i>NOTE:</i> we performed exclusions after the matched cohort was formed, thus, to maintain covariate balance, we eliminated the entire pair of matched exposed-unexposed if at least one of them presented at least one of the abovementioned diagnoses.</p>					

TABLE S7. Unadjusted and propensity-score weighted baseline characteristics of Z-drug-exposed and trazodone-exposed opioid users

Characteristic	Unadjusted			Accounting for Propensity Score Strata		
	Z-drugs plus Opioids	Trazodone plus Opioids	Std Diff ¹	Z-drugs plus Opioids	Trazodone plus Opioids	Std Diff ¹
Number of Individuals	60,751	60,751		60,751	60,750	
Age - years, mean (SD)	49.9 (14.1)	49.8 (15.3)	0.00	49.9 (14.1)	50.1 (15.0)	-0.01
Male sex – n(%)	23,960 (39.4)	20,287 (33.4)	0.12	23,960 (39.4)	24,730 (40.7)	-0.03
Charlson score - median (IQR)	0.5 (1.0)	0.6 (1.1)	-0.10	0.5 (1.0)	0.5 (1.0)	-0.01
Opioid Related Variables						
Opioid prescribed						
Buprenorphine - n (%)**	1,009 (1.7)	1,009 (1.7)	0.00	1,009 (1.7)	1,152 (1.9)	-0.02
Codeine - n (%)**	4,599 (7.6)	4,599 (7.6)	0.00	4,599 (7.6)	4,515 (7.4)	0.00
Fentanyl - n (%)**	14 (0)	13 (0)	0.00	14 (0)	14 (0)	0.00
Hydrocodone - n (%)**	55,134 (90.8)	55,132 (90.8)	0.00	55,134 (90.8)	55,062.3 (90.6)	0.00
Meperidine - n (%)**	3 (0)	6 (0)	0.00	3 (0)	7.5 (0)	0.00
Methadone - n (%)**	0 (0)	0 (0)	0.00	0 (0)	0 (0)	0.00
Morphine - n (%)**	0 (0)	8 (0)	0.00	0 (0)	14.6 (0)	-0.02
Oxycodone - n (%)**	14 (0)	14 (0)	0.00	14 (0)	21.7 (0)	-0.01
Tramadol - n (%)**	0 (0)	4 (0)	0.00	0 (0)	4.3 (0)	0.00
Days' supply for last prescription – mean (SD)	13.6 (12.3)	13.9 (12.2)	-0.02	13.6 (12.3)	14.0 (12.3)	-0.03
Cumulative supply days in the last 180 – mean (SD)	59.9 (67.3)	60.3 (67.1)	0.00	60.0 (67.3)	58.3 (66.2)	0.02
MEQ from the last supply – mean (SD)	558.9 (2359)	554.3 (2360)	0.00	558.9 (2359)	576.7 (2196)	0.00
Cumulative MEQ in the last 180 days – mean (SD)	2565 (14178)	2566 (14178)	0.00	2565 (14178)	2560 (12750)	0.00
Baseline opioid dependence - n (%)	925 (1.5)	1,540 (2.5)	-0.07	925 (1.5)	1066 (1.8)	-0.01
Baseline opioid abuse - n (%)	92 (0.2)	184 (0.3)	-0.02	92 (0.2)	123.3 (0.02)	-0.01
Comorbidities						
Hypertension - n (%)	17,965 (29.6)	18,993 (31.3)	-0.04	17,965 (29.6)	18,498 (30.4)	-0.02
COPD - n (%)	2,753 (4.5)	3,367 (5.5)	-0.05	2,753 (4.5)	2,889 (4.8)	-0.01
Heart failure - n (%)	4,357 (7.2)	4,333 (7.1)	0.00	4,357 (7.2)	4560.8 (7.5)	-0.01
Dementia - n (%)	554 (0.9)	1,471 (2.4)	-0.11	554 (0.9)	693 (1.1)	-0.02

Characteristic	Unadjusted			Accounting for Propensity Score Strata		
	Z-drugs plus Opioids	Trazodone plus Opioids	Std Diff ¹	Z-drugs plus Opioids	Trazodone plus Opioids	Std Diff ¹
Stroke - n (%)	726 (1.2)	1,308 (2.2)	-0.07	726 (1.2)	787 (1.3)	-0.01
Epilepsy or convulsions - n (%)	705 (1.2)	1109 (1.8)	-0.05	705 (1.2)	766 (1.3)	-0.01
Diabetes - n (%)	7,557 (12.4)	8,258 (13.6)	-0.04	7,557 (12.4)	7,717 (12.7)	-0.01
Smoking - n (%)	4,121 (6.8)	5,453 (9.0)	-0.08	4,121 (6.8)	4,211 (6.9)	0.00
Obesity - n (%)	4,170 (6.9)	4,529 (7.5)	-0.02	4,170 (6.9)	4,378 (7.2)	-0.01
Renal failure - n (%)	2,662 (4.4)	3,360 (5.5)	-0.05	2,662 (4.4)	2,714 (4.5)	0.00
Chronic Liver Disease - n (%)	797 (1.3)	1,028 (1.7)	-0.03	797 (1.3)	834.5 (1.4)	0.00
Asthma - n (%)	3,211 (5.3)	3,713 (6.1)	-0.03	3,211 (5.3)	3,263 (5.4)	0.00
Ischemic Heart Disease - n (%)	4,357 (7.2)	4,333 (7.1)	0.00	726 (1.2)	789 (1.3)	0.00
Parkinson Disease - n (%)	158 (0.3)	284 (0.5)	-0.03	158 (0.3)	168 (0.3)	0.00
Allergic Rhinitis - n (%)	4,220 (6.9)	4,011 (6.6)	0.01	4,220 (6.9)	3,828 (6.3)	0.03
Pancreatitis - n (%)	329 (0.5)	436 (0.7)	-0.03	329 (0.5)	352 (0.6)	0.00
Urinary Incontinence - n (%)	668 (1.1)	807 (1.3)	-0.01	668 (1.1)	687 (1.1)	0.00
Pain Related Conditions						
Neuropathic pain - n (%)	9,893 (16.3)	10,400 (17.1)	-0.02	9,893 (16.3)	10,254 (16.9)	-0.01
Back pain - n (%)	20,497 (33.7)	22,166 (36.5)	-0.06	20,497 (33.7)	20,906 (34.4)	-0.01
Neck pain - n (%)	8,858 (14.6)	9,876 (16.3)	-0.05	8,858 (14.6)	9,078 (14.9)	-0.01
Joint pain - n (%)	18,645 (30.7)	18,119 (29.8)	0.02	18,645 (30.7)	19,911 (31.5)	-0.02
Tendon/Bursal pain - n (%)	6,924 (11.4)	5,881 (9.7)	0.06	6,924 (11.4)	7,173 (11.8)	-0.01
Musculoskeletal injury (severe) - n (%)	4,216 (6.9)	2,716 (4.5)	0.10	4,216 (6.9)	4,612 (7.6)	-0.03
Urinary calculus - n (%)	3,498 (5.8)	3,572 (5.9)	0.00	3,498 (5.8)	3,650 (6.0)	-0.01
Dental pain - n (%)	362 (0.6)	551 (0.9)	-0.03	362 (0.6)	367 (0.6)	0.00
Pain not elsewhere specified - n (%)	5,036 (8.3)	5,406 (8.9)	-0.02	5,036 (8.3)	5,300 (8.7)	-0.01
Generalized pain - n (%)	407 (0.7)	605 (1.0)	-0.03	407 (0.7)	428 (0.7)	0.00
Pain related to psychological factors - n (%)	153 (0.3)	239 (0.4)	-0.02	153 (0.3)	159 (0.3)	0.00
Fibromyalgia - n (%)	3,787 (6.2)	5,074 (8.4)	-0.08	3,787 (6.2)	3,878 (6.4)	0.00
Migraine - n (%)	7,260 (12.0)	9,403 (15.5)	-0.10	7,260 (12.0)	7,332 (12.1)	0.00
Open wound lesion - n (%)	863 (1.4)	1,062 (1.7)	-0.02	863 (1.4)	981 (1.6)	-0.01
Rheumatoid Arthritis - n (%)	1,185 (2.0)	1,169 (1.9)	0.01	1,185 (2.0)	1,261 (2.1)	0.00
Psychiatric Related Conditions						

Characteristic	Unadjusted			Accounting for Propensity Score Strata		
	Z-drugs plus Opioids	Trazodone plus Opioids	Std Diff ¹	Z-drugs plus Opioids	Trazodone plus Opioids	Std Diff ¹
Unspecified mental disorder - n (%)	343 (0.6)	793 (1.3)	-0.07	343 (0.6)	420 (0.7)	-0.02
Depression diagnosis - n (%)	8,951 (14.7)	17,250 (28.4)	-0.34	8,951 (14.7)	9389 (15.5)	-0.02
ADHD - n (%)	1,226 (2.0)	1,751 (2.9)	-0.06	1,226 (2.0)	1,295 (2.1)	-0.01
Bipolar Disorder - n (%)	1,183 (1.9)	2,220 (3.7)	-0.10	1,183 (1.9)	1,320 (2.2)	-0.01
Anxiety Disorder - n (%)	7,329 (12.1)	12,412 (20.4)	-0.23	7,329 (12.1)	7,608 (12.5)	-0.01
Insomnia diagnosis - n (%)	8,851 (14.6)	11,923 (19.6)	-0.13	8,851 (14.6)	8,807 (14.5)	0.00
Schizophrenia diagnosis - n (%)	333 (0.5)	855 (1.4)	-0.10	333 (0.5)	424 (0.7)	-0.01
Personality disorder - n (%)	221 (0.4)	441 (0.7)	-0.04	221 (0.4)	253 (0.4)	0.00
Drug abuse dependence - n (%)	973 (1.6)	2,005 (3.3)	-0.11	973 (1.6)	1121 (1.8)	-0.02
Alcohol abuse or dependence - n (%)	747 (1.2)	1,794 (3.0)	-0.13	747 (1.2)	902 (1.5)	-0.02
Sedative abuse or dependence - n (%)	83 (0.1)	175 (0.3)	-0.04	83 (0.1)	109 (0.2)	-0.01
Past suicide attempt - n (%)	204 (0.4)	644 (1.1)	-0.10	204 (0.4)	286 (0.5)	-0.02
Psychotropic Concomitant Medication						
Benzodiazepine use - n (%)	19,963 (32.9)	24,192 (39.8)	-0.14	19,963 (32.9)	20,185 (33.2)	0.00
Benzodiazepine equivalent dose – mean (SD)	57.9 (386)	68.7 (394)	-0.03	57.9 (386)	60.9 (364)	0.00
Antidepressants (SSRI) – n (%)	21,526 (35.4)	31,919 (52.5)	-0.35	21,526 (35.4)	20,946 (34.5)	0.02
Lithium - n (%)	263 (0.4)	446 (0.7)	-0.04	263 (0.4)	287 (0.5)	0.02
Antipsychotics - n (%)	2,324 (3.8)	4,145 (6.8)	-0.13	2,324 (3.8)	2,595 (4.3)	-0.02
Muscle relaxants - n (%)	15,981 (26.3)	17,850 (29.4)	-0.07	15,981 (26.3)	16,290 (26.8)	-0.01
Gabapentinoids - n (%)	6,894 (11.3)	9,121 (15.0)	-0.11	6,894 (11.3)	7,015 (11.5)	0.00
Healthcare use Measures						
No. Hospitalizations in the past 180 days – mean (SD)	0.2 (0.6)	0.3 (0.6)	-0.07	0.2 (0.6)	0.2 (0.6)	-0.02
No. Physician visits in the past year - mean (SD)	5.4 (4.5)	5.9 (5.0)	-0.11	5.4 (4.5)	5.5 (4.9)	-0.02
No. Psychiatric visits - mean (SD)	0.4 (1.1)	0.6 (1.4)	-0.22	0.4 (1.1)	0.4 (1.1)	-0.02
No. Psychiatric hospitalizations – mean (SD)	0.0 (0.1)	0.0 (0.2)	-0.12	0.0 (0.1)	0.0 (0.2)	-0.03
No. ED visits – mean (SD)	0.5 (1.3)	0.6 (1.7)	-0.11	0.5 (1.3)	0.5 (1.3)	-0.02

Characteristic	Unadjusted			Accounting for Propensity Score Strata		
	Z-drugs plus Opioids	Trazodone plus Opioids	Std Diff ¹	Z-drugs plus Opioids	Trazodone plus Opioids	Std Diff ¹
No. ICD diagnoses (3rd digit level) – mean (SD) [^]	10.1 (7.7)	11.3 (8.6)	-0.14	10.1 (7.7)	10.4 (8.1)	-0.03
Total No. medications% – mean (SD)	6.6 (4.9)	7.6 (5.2)	-0.20	6.6 (4.9)	6.6 (4.8)	-0.01
Hospitalized past month - n (%)**	5,255 (8.7)	5,255 (8.7)	0.00	5,255 (8.7)	5,033 (8.3)	0.01

SSRI: selective serotonin reuptake inhibitors; COPD: chronic obstructive pulmonary disease; SD: standard deviation; IQR: interquartile range; MEQ: Morphine Equivalents; ADHD: Attention Deficit and Hyperactivity Disorder; No.: Number of; ED: Emergency Department; ICD9: International Classification of Diseases 9th Edition.

% Other than opioids and/or z-drugs; [^] Not including insomnia; ** Variables used in the matching process.

Std Diff estimated as $\frac{\bar{x}_{exp} - \bar{x}_{ref}}{\sqrt{\frac{s_{exp}^2 + s_{ref}^2}{2}}}$ where s² represents the sample variance in both exposed and unexposed groups.

TABLE S8. Specific anxiety and depression diagnoses

Characteristic	Unadjusted		Accounting for Propensity Score Strata			
	Z-drugs plus Opioids (n=510,529)	Opioids alone (n=510,529)	Std Diff ¹	Z-drugs plus Opioids (n=510,527)	Opioids alone (n=510,529)	Std Diff ¹
	%	%		%	%	
<i>Anxiety diagnoses</i>						
Unspecified Anxiety	0.2	0.1	0.03	0.2	0.2	0.00
Phobic Disorders	0.3	0.2	0.02	0.3	0.3	0.00
OCD	7.2	4.6	0.11	7.2	7.5	0.00
PTSD	0.6	0.3	0.04	0.6	0.5	0.00
<i>Depression diagnoses</i>						
MDD – Single Episode	2.3	1.3	0.07	2.3	2.3	0.00
MDD – Recurrent Episode	3.6	1.9	0.10	3.6	3.5	0.01
Adjustment disorder with Depressed mood	0.7	0.4	0.04	0.7	0.6	0.01
Dysthymic Disorder	1.8	1.2	0.05	1.8	2.0	0.01

Abbreviations: IQR (Interquartile range), SD: Standard deviation, Std Diff: standardized difference, OCD: Obsessive compulsive Disorder, PTSD: Post-Traumatic Stress Disorder, MDD: Major Depressive Disorder.

Appendix 1. Full description of cohort building and matching procedure.

The source cohort was formed at the episode level by selecting all prescriptions of opioids within the IBM MarketScan data between 2003-2017.

Within this source cohort, we identified all incident Z-drug prescriptions for patients aged 15-85. We defined incident z-drug prescriptions as any prescription of zolpidem, zopiclone or eszopiclone not preceded by any prescription of these drugs in the last 180 days. In order to identify co-prescription episodes, we next required an opioid filling within the 14 days prior to the incident Z-drug prescription. If there was more than one opioid filling within the 14-day window, the one closest in time to the Z-drug prescription was considered the qualifying prescription. The exposed cohort was built at the episode level: an individual could contribute multiple co-prescription episodes as long as the cohort entry criteria were met for each episode. The date of the incident Z-drug prescription was defined as the index date. The number of days between the qualifying opioid prescription and the qualifying Z-drug prescription ('opioid-days', which by design could not be greater than 14 days) was estimated for each episode. We applied the following exclusion criteria: cancer/palliative care diagnosis, lack of continuous enrolment for 180 days prior to index date, and non-conventional opioid formulations (see eTable 7). Finally, if an individual contributed more than one exposed episode in a given calendar year, we randomly selected one episode.

Next, we constructed the reference cohort. Within the source cohort, we first identified all opioid prescriptions in patients aged 15-85. The date of the opioid prescription was defined as the index date. We then applied the same exclusion criteria as for the exposed episodes to each reference episode: cancer/palliative care diagnosis, lack of continuous enrolment for 180 days prior to the index date, and non-conventional opioid formulation (see eTable 9). All eligible reference episodes were available for matching to the exposed episodes.

The first step to assemble the matched cohort was to order all exposed episodes chronologically based on their index date (i.e., the date of the qualifying Z-drug prescription). We then selected the chronologically first exposed episode and randomly selected a reference episode during the same calendar year, with matching on:

- Opioid agent of the last prescription (if patients filled prescriptions for multiple opioids on the same day, only one was required to match);
- Morphine equivalents (MEQ) of the qualifying opioid prescription (± 50);
- Hospitalization within the last 30 days;
- Cumulative number of days' supply for opioids in the last 180 days (± 5 days);
- Cumulative MEQ for all opioid prescriptions in the last 180 days (± 100).

These matching factors were selected a priori as we considered them to be the strongest potential confounders. We set aside the exposed and the matched reference episode and removed these patients from the pool so that neither of them could contribute any further episodes. Consequently, if an exposed patient contributed episodes in different calendar years, the first chronological episode was used for matching. We then selected the chronologically next exposed episode and repeated these steps iteratively until all exposed episodes were matched to a referent episode. Since patients could only contribute one exposed or referent episodes, the final cohort was formed at the patient (as opposed to the episode) level.

Appendix 2. Fine Propensity Score Stratification analysis.

- We fitted the following logistic regression analysis:
 $\text{Logit}[\text{Pr}(\text{Z-drug use})] = \text{intercept} + \text{all covariates included in Table 1 without interaction terms or higher-order polynomials for continuous variables.}$
- We obtained the predicted probabilities of receiving a Z-drug from the above model for every individual in our dataset (i.e., the propensity score).
- We excluded patients in the non-overlapping regions of the PS distribution of exposed and referent groups.
- We created 50 equally-sized strata based on the distribution of the PS in the exposed group.
- We assigned each reference subject to its corresponding stratum based on their PS value.
- Weighted regression models were used to derive an adjusted effect after stratification, in which the weights were calculated as follows:

Cohort	Weight
Exposed	1
Unexposed	$(N_{\text{exposed in strata } i} / N_{\text{total exposed}}) / (N_{\text{unexposed in strata } i} / N_{\text{total unexposed}})$

The unexposed weights were meant to scale up or down to match the sum of exposed individuals in a given stratum.

- Final model (Cox Proportional Hazard Regression Model)

Outcome (overdose) = z-drug use ;

Weighted by the above computed weights.

Appendix 3. Description of pooled logistic regression analysis used to estimate survival curves and to calculate absolute survival differences at 30-days.

To estimate the adjusted 30-day survival curves, we fitted a discrete-time hazards model with 1-day periods as follows:

$$\text{Logit}[\text{Pr}(\text{Overdose}=0_{\text{day}=t} \mid \text{Overdose}=0_{\text{day}=t-1})] = \beta_{0,t} + \beta_1 \text{Treatment} + \beta_2 \text{Day} + \beta_3 \text{Day}^2 + \beta_4 \text{Day} * \text{Treatment} + \beta_5 \text{Day}^2 * \text{Treatment}$$

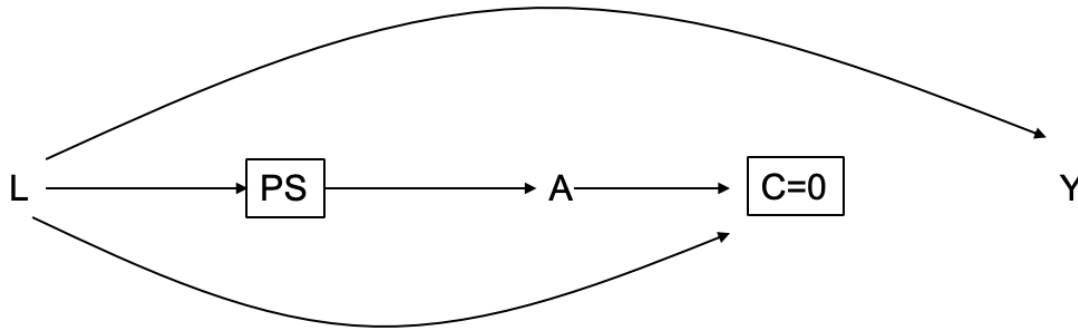
Where $\beta_{0,t}$ is the time-varying intercept, and β_1 from the pooled logistic regression will approximate the HR from a Cox Proportional Hazard Regression model provided the event is rare within time interval (i.e., one-day). This model was weighted by the inverse probability of treatment given the baseline confounders (i.e., using the abovementioned propensity score) as follows:

Cohort	Weight
Exposed	0.5 / PS
Unexposed	0.5 / (1-PS)

PS=propensity score

For each individual, under each value of treatment, this model was used to predict the daily probability of overdose survival in a pseudopopulation without confounding by baseline variables. Survival at day t was calculated as the product of daily conditional survival probabilities up to day t. We used this method to obtain the adjusted survival curves and also to compute the absolute survival differences at 30 days.

Appendix 4. Description of the as treated analysis, including calculation of inverse probability of treatment and censoring weights.



L: measured confounders for the association between z-drug use and overdose and risk factors of overdose associated with adherence; A: exposure (z-drug use); Y: outcome (overdose); C: Censoring due to lack of adherence to treatment strategy (i.e., opioid plus z-drug in the exposed group and opioid in the reference group).

The as-treated analysis is conducted conditioning on a post-treatment initiation variable (C) which induces selection bias due to L even after accounting by Propensity Score. An unbiased estimate of the as-treated effect needs to condition on L.

Model to calculate stabilized weights for treatment:

- 1) Weights denominator model:
 - Concomitant z-drug use= All baseline covariates shown in Table 1 (L1).
 - This is the same model as in the propensity score estimation.
 - Predicted values from this model saved as “pred”.

Cohort	Weight
Exposed	0.5 / pred
Unexposed	0.5 / (1-pred)

Model to calculate stabilized weights for censoring:

- 2) Weights numerator model:
 - Uncensored= .
 - This models Pr(being_uncensored) by using PROC LOGISTIC without Descending option.
 - Numerator = predicted values from the above model.
- 3) Weights denominator model:
 - Uncensored= All baseline predictors of censoring and outcome (L2).
 - Denominator = predicted values from the above model.

Cohort	Weight
Censored	0
Uncensored	Numerator / Denominator

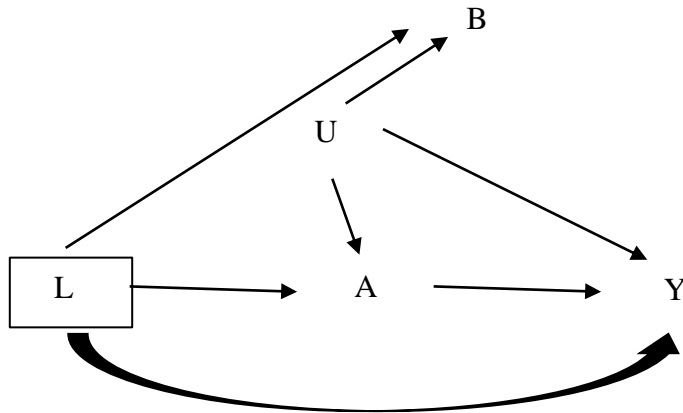
- 4) Final Weights:
- Multiplication of treatment * censoring weights

MSM main model with weights:

- Outcome (overdose) = concomitant z-drug use

This model is weighted by the above-specified stabilized weights

Appendix 5. Negative Control Exposure using Proton Pump Inhibitors.



L: measured confounders; U: unmeasured confounders (underlying clinical comorbidities); A: exposure (z-drug use); Y: outcome (overdose); B: Negative Exposure Control (Proton-Pump Inhibitors)

B does not cause Y (no arrow) and B is “U-Comparable” to A (shares the unmeasured confounders). The finding of an association between B and Y – given that there is no arrow between these variables – has to be due a backdoor path through U. In this case, U represents unmeasured confounding due to higher burden of medical comorbidities, diagnoses and procedures (i.e., frailty). Because adult patients with multiple comorbidities are frequently prescribed PPI, this exposure would capture the association with U and we do not anticipate an increased risk of overdose associated with the concomitant use of these drugs and opioids, as compared to opioids alone.

Level of Adjustment	Exposed to PPI agents plus opioids		Exposed to opioids alone		HR (95% CI)
	Events	Person-years	Events	Person-years	
30-day Intention-to-treat Opioid and/or psychotropic overdose (primary outcome)					
Unadjusted	142	57851.19	89	55623.52	1.54 (1.18 - 2.01)
Fine PS stratification	142	57851.19	89	55623.52	1.04 (0.82 - 1.32)