

1 **SUPPLEMENTARY INFORMATION**
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eMethods 1 - MarketScan data extraction

The MarketScan® cohort is one of the largest administrative claims data samples in the United States used in analysis of OUD treatment outcomes. This represents claims for insured active employees, early (non-Medicare) retirees, and dependents insured by employer-sponsored plans as well as Medicaid insurance holders (Mintz et al., 2020). As previously described, private insurance data in MarketScan spans all 50 states, whereas MarketScan determined the states included in the Medicaid data (Mintz et al., 2020). Information about the states included in the Medicaid dataset was not made available to us. It was also unknown to us whether the states remained constant over the total period of observation, from 2006 to 2016.

Data were available from January 1, 2006 to December 31, 2016 for the commercial database and between January 1, 2011 and December 31, 2016 for the Medicaid database. Paid claims and encounter data were linked to detailed patient information across different sites, types of providers, and over time. Unique insurance enrollee ID numbers were available to link claims from the same individual. A unique family ID number was available to link family members on the same insurance plan. This ultimately captured longitudinal person-specific information on clinical utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug services.

References:

Mintz C.M. PNJ, Sahrman J.M., Borodovsky J.T., Glaser P.E.A., Bierut L.J., Grucza R.A. Age disparities in six-month treatment retention for opioid use disorder. *Drug and Alcohol Dependence* 2020;213

28 **eMethods 2 – Characteristics of Individuals With and Without Drug-Related**
29 **Poisonings**

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31 We sought to compare opioid use disorder (OUD) treatment characteristics between those who
32 experienced poisoning and peers without history of poisoning events. To accomplish this, we obtained a
33 random sample of participants who never experienced poisoning events in the MarketScan analysis (any
34 time between January 1, 2006 and December 31, 2016), for which we compared descriptive statistics of
35 those who had poisoning events. A random date was selected among participants who never had
36 poisonings in order to define window of observation.

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38 We described differences between participants who had poisonings and those who did not; we compared
39 our final sample of OUD patients with poisonings with a random sampling of OUD patients (N=30,760)
40 who never had a poisoning. On the **individual person level**, eTable 3 shows that patients with a drug-
41 related poisoning history had a similar prevalence of using (within a year of poisoning) buprenorphine but
42 higher prevalence of using benzodiazepines or Z drugs (56% vs 40%) than peers without poisonings in
43 the 1 year before and after index drug-related poisoning.

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45 To evaluate the level of severity of OUD between our analytic cohort and OUD patients who had never
46 experienced drug-related poisoning, we compared, at the **person-days level**, participants who had a
47 history of drug-related poisoning to their peers who never had poisonings (eTable 4). We observed a
48 higher prevalence of claims for benzodiazepine (both short-acting and long-acting) and Z drugs among
49 OUD patients with a poisoning history than peers without poisoning, although persons without overdose
50 exhibited higher prevalence of claims for buprenorphine treatment (22.1% vs 15.6%). Across all person-
51 days of treatment, we calculated the mean daily doses of buprenorphine and benzodiazepines. Between
52 treatment days for individuals who had poisonings and their peers without poisonings, we observed
53 similar mean daily doses of buprenorphine (15.4 mg among OUD patients who had poisonings vs 15.2
54 mg among those who never had poisonings) and for any benzodiazepine or Z drug (25.9 diazepam mg
55 equivalents vs 22.1 diazepam mg equivalents, respectively), despite higher prevalence of these
56 medications in the poisoning group.

58 **eMethods 3 – Assessment of Time-Varying Factors and Procedure for Time-**
59 **Varying, Multiple Window Sensitivity Analysis**

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61 We controlled for time relative to the index poisoning event by including the number of days before or
62 after the index drug-related poisoning as a covariate using restricted cubic spline function to allow for a
63 flexible association between time and outcome data. Similarly, we controlled for secular time trends
64 (Fixed Effects 2006; Mittleman et al. 2014), using calendar-time or date as a covariate as a restricted
65 cubic spline. Because unmeasured time-varying factors may be associated with both medication
66 utilization and drug-related poisoning, we conducted a sensitivity analysis with eight different windows of
67 observation, with the objective of assessing the degree to which such time-varying factors may bias our
68 estimates of drug risk or protective effects.

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70 Because unmeasured time-varying factors may be associated with both medication utilization and drug-
71 related poisoning, we conducted a sensitivity analysis with different windows of observation, with the
72 objective of assessing the degree to which such time-varying factors may bias our estimates of drug risk
73 or protective effects. Our primary analyses utilized a maximum observation window of one year before
74 and after index poisoning; participants were not required to have data for the full observation window. To
75 assess impact of time-varying factors in our analysis, we repeated our regression models on eight
76 alternative windows of observation (each spanning 400 days of time in total) that fell within the original
77 period of observation:

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- 79 1. 360 days before index poisoning, 40 days after index poisoning
 - 80 2. 320 days before index poisoning, 80 days after index poisoning
 - 81 3. 280 days before index poisoning, 120 days after index poisoning
 - 82 4. 240 days before index poisoning, 160 days after index poisoning
 - 83 5. 200 days before index poisoning, 200 days after index poisoning
 - 84 6. 160 days before index poisoning, 240 days after index poisoning
 - 85 7. 120 days before index poisoning, 280 days after index poisoning
 - 86 8. 80 days before index poisoning, 320 days after index poisoning

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88 As shown in eFigure 1, which illustrates the results of Model 10 (Table 3), we observed no significant
89 variation in point estimates for drug related poisoning risk across these 8 windows of observation.

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92 References

93 Fixed Effects Regression Methods in SAS. SUGI 31 Proceedings; 2006; San Francisco, CA.

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95 Mittleman MA, Mostofsky E. Exchangeability in the case-crossover design. *Int J Epidemiol*
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eTable 1. Overview of Diagnosis Codes for Opioid Use Disorder Diagnosis, Drug-Related Poisonings, Treatment Services, and Medications

eTable 1A. Diagnosis Codes for Opioid Use Disorder and Drug-Related Poisonings

Diagnosis	ICD-9/-10-CM diagnosis codes
Opioid Use Disorder	305.5, 304.0, 304.7 F11
Drug-Related Poisoning	'T40' 'T41' 'T42' 'T43' 'T44' 'T45' 'T46' 'T47' 'T48' 'T49' 'T50' 'T51' 'T52' 'T53' 'T54' 'T55' 'T56' 'T57' 'T58' 'T59' 'T60' 'T61' 'T62' 'T63' 'T64' 'T65' '960' '961' '962' '963' '964' '965' '966' '967' '968' '969' '970' '971' '972' '973' '974' '975' '976' '977' '978' '979' '980' '981' '982' '983' '984' '985' '986' '987' '988' '989' 'E850' 'E851' 'E852' 'E853' 'E854' 'E855' 'E856' 'E857' 'E858' 'E860' 'E861' 'E862' 'E863' 'E864' 'E865' 'E866' 'E867' 'E868' 'E869' 'E950' 'E951' 'E952' 'E962' 'E972' 'E975' 'E976' 'E980' 'E981' 'E982'

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eTable 1B. Procedural Codes for Opioid Use Disorder Treatment Services

Coding System	Procedural Code
Healthcare Common Procedure Coding System	H0001 H0002 H0003 H0004 H0005 H0006 H0007 H0008 H0009 H0010 H0011 H0012 H0013 H0014 H0015 H0016 H0017 H0018 H0019 H0020 H0021 H0022 H0023 H0024 H0025 H0026 H0027 H0028 H0029 H0030 H0031 H0032 H0033 H0034 H0035 H0036 H0037 H0038 H0039 H0040 H0041 H0042 H0043 H0044 H0045 H0046 H0047 H0048 H0049 H0050 H1000 H1001 H1002 H1003 H1004 H1005 H1010 H1011 H2000 H2001 H2010 H2011 H2012 H2013 H2014 H2015 H2016 H2017 H2018 H2019 H2020 ^a H2021 H2022 H2023 H2024 H2025 H2026 H2027 H2028 H2029 H2030 H2031 H2032 H2033 H2034 H2035 H2036 H2037 J2315 ^b T1002 T1006 T1007 T1012 T1016 T2048
Current Procedural Terminology	90791 90832 90834 90837 90840 90845 90846 90847 90849 90853 90839 90801 90802 90804 90806 90808 90810 90812 90814 90816 90818 90821 90823 90826 90828 90857
International Statistical Classification of Diseases	9464 9465 ^c 9466 9467 9468 ^d 9469 HZ2ZZZZ ^e HZ30ZZZ HZ31ZZZ HZ32ZZZ HZ33ZZZ HZ34ZZZ HZ35ZZZ HZ36ZZZ HZ37ZZZ HZ38ZZZ HZ39ZZZ HZ3BZZZ HZ40ZZZ HZ41ZZZ HZ42ZZZ HZ43ZZZ HZ44ZZZ HZ45ZZZ HZ46ZZZ HZ47ZZZ HZ48ZZZ HZ49ZZZ HZ4BZZZ

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^arefers to methadone administration. ^brefers to extended-release naltrexone administration. ^crefers to detoxification services. Services without footnotes denote psychosocial treatment.

111 eTable 1C. National Drug Codes Used for Identification of Opioid Use Disorder
 112 Pharmacy Claims

Medication	National Drug Code
Buprenorphine	00054017613 00054017713 00054018813 00054018913 00093537856 00093537956 00093572056 00093572156 00228315303 00228315403 00228315473 00228315503 00228315573 00228315603 00378092393 00378092493 00406192303 00406192403 00490005130 12496120201 12496120203 12496120401 12496120403 12496120801 12496120803 12496121201 12496121203 12496127802 12496128302 12496130602 12496131002 16590066630 16590066730 23490927003 35356000430 38779088800 38779088801 38779088803 38779088809 42291017430 42291017530 43063018430 49452129203 49452825301 49452825302 49452825303 49452825304 49999039515 49999063830 49999063930 50383028793 50383029493 50383092493 50383093093 51927101200 52959030430 52959074930 54123011430 54123091430 54123092930 54123095730 54123098630 54569573900 54569573901 54569573902 54569639900 54868570700 54868570701 54868575000 55700014730 59385001201 59385001230 59385001401 59385001430 59385001601 59385001630 60429058630 60429058730 62991158301 62991158302 62991158303 62991158304 63275992202 63370090506 63370090509 63370090510 63370090515 63874108503 63874117303 65162041503 65162041603 68071151003 68308020830
Naltrexone (Oral)	00056001130 00056001170 00185003901 00185003930 00406117001 00406117003 00555090201 00555090202 16729008101 16729008110 38779088703 38779088704 38779088705 38779088706 42291063230 47335032683 47335032688 49452483501 49452483502 51224020630 51224020650 51285027501 51285027502 51552073701 51552073702 51927354800 51927360200 51927437700 52152010502 52152010530 52372075102 62991124301 62991124302 62991124303 62991124304 63370015810 63370015815 63370015825 63370015835 68084029121 68094085362
Extended-Release Naltrexone	63459030042 65757030001

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eTable 2. Conversion Factors for the Standardization of Benzodiazepine Strength

eTable 2A. Strength of Short Acting Benzodiazepines in Diazepam Equivalent Milligrams (alprazolam, oxazepam, triazolam, estazolam, temazepam, and midazolam)

ALPRAZOLAM	
Diazepam Equivalent Milligrams	Strength
2.5	0.25 MG
5	0.5 MG
10	1 MG
10	1 MG/1 ML
20	2 MG
30	3 MG
LORAZEPAM	
Diazepam Equivalent Milligrams	Strength
2.5	0.5 MG
5	1 MG
10	2 MG
10	2 MG/1 ML
20	4 MG/1 ML
OXAZEPAM	
Diazepam Equivalent Milligrams	Strength
3	10 MG
4.5	15 MG
9	30 MG
TRIAZOLAM	
Diazepam Equivalent Milligrams	Strength
5	0.125 MG
10	0.25 MG
ESTAZOLAM	
Diazepam Equivalent Milligrams	Strength
5	1 MG
10	2 MG
TEMAZEPAM	
Diazepam Equivalent Milligrams	Strength
4.5	15 MG
6.75	22.5 MG
9	30 MG
2.25	7.5 MG

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MIDAZOLAM	
Diazepam Equivalent Milligrams	Strength
1	1 MG/1 ML
2	2 MG/1 ML
5	5 MG/1 ML

eTable 2B. Strength of long acting Benzodiazepines in diazepam equivalent milligrams (chlordiazepoxide, diazepam, clobazam, clonazepam, flurazepam, and quazepam)

CLONAZEPAM	
Diazepam Equivalent Milligrams	Strength
2.5	0.125 MG
5	0.25 MG
10	0.5 MG
20	1 MG
40	2 MG
DIAZEPAM	
Diazepam Equivalent Milligrams	Strength
10	10 MG
10	10 MG; NA
15	15 MG; NA
2	2 MG
2.5	2.5 MG; NA
20	20 MG; NA
5	5 MG
5	5 MG/1 ML
5	5 MG/5 ML
CHLORDIAZEPOXIDE	
Diazepam Equivalent Milligrams	Strength
2	10 MG
2.5	12.5 MG-5 MG
5	25 MG
5	25 MG-10 MG
1	5 MG
CLOBAZAM	
Diazepam Equivalent Milligrams	Strength
5	10 MG
1.25	2.5 MG/1 ML
10	20 MG
2.5	5 MG

FLURAZEPAM	
Diazepam Equivalent Milligrams	Strength
4.5	15 MG
9	30 MG
QUAZEPAM	
15	15 MG

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eTable 2C. Strength of Selective Benzodiazepine Receptor Modulators in Diazepam Equivalent Milligrams (zolpidem, eszopiclone, zaleplon)

ZOLPIDEM	
Diazepam Equivalent Milligrams	Strength
0.875	1.75 MG
5	10 MG
6.25	12.5 MG
1.75	3.5 MG
2.5	5 MG
2.5	5 MG/0.1 ML
3.125	6.25 MG
3.125	62.5 MG; 5 MG
ESZOPICLONE	
Diazepam Equivalent Milligrams	Strength
1.67	1 MG
3.34	2 MG
5.01	3 MG
ZALEPLON	
Diazepam Equivalent Milligrams	Strength
5	10 MG
2.5	5 MG

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eTable 3. Individual Level Comparison of Opioid Use Disorder Treatment Characteristics, in the 1 year Before and After Index Drug-Related Poisoning, between Participants with and without History of Drug-Related Poisoning

	Individuals with Overdoses		Individuals without Overdoses	
	N=23,036 Participants		N=30,760 Participants	
	Number of Individuals	%	Number of Individuals	%
Buprenorphine Use	16,451	71.41	22,055	71.7
Low Dose, ≤12 mg daily	9,469	41.11	12,163	39.54
High Dose, > 12 mg daily	11,690	50.75	16,007	52.04
Use of any Benzodiazepines or Z drugs	12,890	55.96	12,154	39.51
Use of any Benzodiazepines excluding Z drugs	11,839	51.39	10,642	34.6
Low Dose (≤ 30 diazepam equivalent mg daily)	10,356	44.96	9,260	30.1
High Dose (> 30 diazepam equivalent mg daily)	5,227	22.69	3,372	10.96
Use of Short Acting Benzodiazepine	9,292	40.34	7,749	25.19
Alprazolam	6,210	26.96	5,187	16.86
Lorazepam	4,433	19.24	2,920	9.49
Oxazepam	130	0.56	95	0.31
Triazolam	248	1.08	227	0.74
Estazolam	19	0.08	10	0.03
Temazepam	1,127	4.89	730	2.37
Midazolam	47	0.2	16	0.05
Use of Long Acting Benzodiazepine	6,660	28.91	5,243	17.04
Clonazepam	3,885	16.86	2,678	8.71
Diazepam	3,612	15.68	2,970	9.66
Chlordiazepoxide	206	0.89	105	0.34
Clobazam	1	0	0	0
Flurazepam	33	0.14	15	0.05
Quazepam	2	0.01	0	0
Use of Z Drugs	5,068	22	4,278	13.91
Zolpidem	4,640	20.14	3,862	12.56
Eszopiclone	1,025	4.45	715	2.32
Zaleplon	216	0.94	139	0.45
Methadone Use	420	1.82	439	1.43
Naltrexone XR Use	746	3.24	395	1.28

Naltrexone Use	1,449	6.29		663	2.16
SSRI Use	10,286	44.65		9,321	30.3
Mean Age	30.05	12.15		31.58	11.11
Mean Year of Birth	1980			1979	
Sex (Male)	11,713	50.85		17,149	55.75
Mean Days of Observation	600.09	147.06		584.94	140.92
Relationship of Patient to Primary Beneficiary					
Employee	4,345	28.30		10,567	47.04
Spouse	3,746	24.40		5,397	24.02
Child/other	7,263	47.30		6,501	28.94
Medicaid	7,682	33.35		8,295	26.97

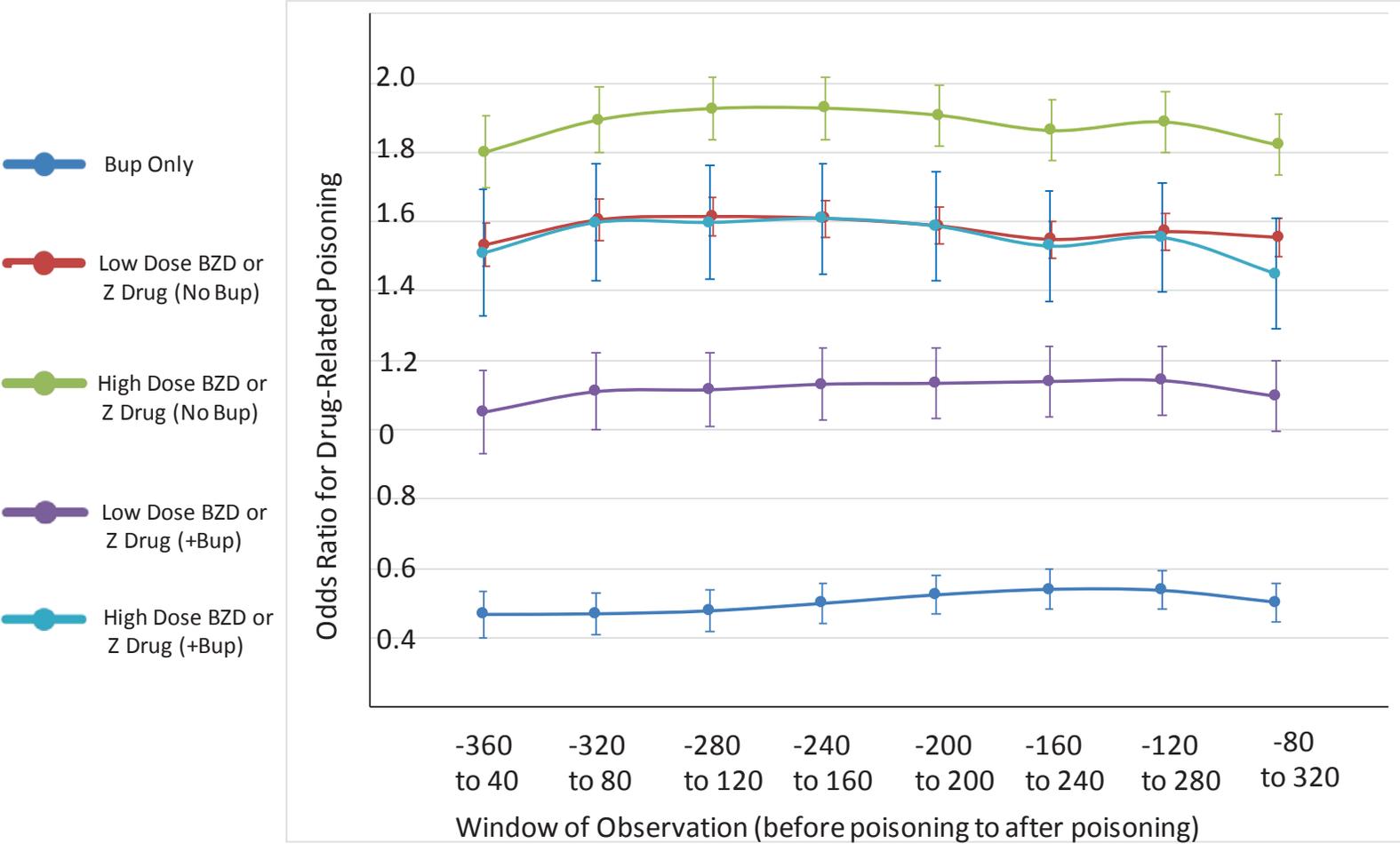
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eTable 4. Person-Days Level Comparison of Opioid Use Disorder Treatment Characteristics Between Participants With and Without History of Drug-Related Poisoning

		Among Individuals with Overdoses		Among Individuals without Overdoses	
		14,213,075 Treatment Days		17,936,977 Treatment Days	
		Person-Days	(%)	Person-Days	(%)
Treatment Days Marked by Drug-Related Poisoning		26,243	0.18	0	100
Days Treated with Buprenorphine		2,210,927	15.56	3,969,804	22.13
Mean Dose (mg daily)	(sd)	15.44	7.31	15.18	7.52
Low-dose, ≤12 mg daily		758,261	5.33	1,436,019	8.01
High-dose, > 12 mg daily		1,367,893	9.62	2,356,035	13.14
Days Treated with SSRIs		1,715,489	12.07	1,579,164	8.8
Days Treated with Benzodiazepines or Z drugs		2,493,800	17.55	2,108,461	11.75
Mean Dose (diazepam equivalent mg daily)	(sd)	23.39	25.88	19.47	22.07
Days Treated with Benzodiazepines excluding Z drugs		1,968,944	13.85	1,592,414	8.88
Mean Dose (diazepam equivalent mg daily)	(sd)	27.58	26.98	23.59	23.46
Low-dose, ≤ 30 diazepam equivalent mg daily)		1,453,110	10.22	1,277,170	7.12
High-dose, > 30 diazepam equivalent mg daily)		515,834	3.63	315,244	1.76
Days Treated with Short Acting Benzodiazepines		1,584,424	11.15	1,272,339	7.09
Mean Dose (diazepam equivalent mg daily)	(sd)	25.33	20.53	22.19	19.18
Days Treated with Long Acting Benzodiazepines		452,820	3.19	357,800	1.99
Mean Dose (diazepam equivalent mg daily)	(sd)	31.28	38.10	26.08	32.33
Days Treated with Z Drugs		825,610	5.81	722,677	4.03
Mean Dose (diazepam equivalent mg daily)	(sd)	4.88	1.24	4.83	1.07

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eFigure 1. Time varying, multiple-window sensitivity analysis for interaction between benzodiazepine and buprenorphine on drug-related poisonings (Model 10, Table 3)