



# THE JOURNAL OF CLINICAL PSYCHIATRY

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## **Supplementary Material**

**Article Title:** Association of Bupropion, Naltrexone, and Opioid Agonist Treatment With Stimulant-Related Admissions Among People With Opioid Use Disorder: A Case-Crossover Analysis

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## **Disclaimer**

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

## Supplementary Methods:

Secondary analyses were conducted stratifying patients by sex, age (under 30, 30+ years), and year of insurance enrollment (2006-2011 vs 2012-2015)(Supplementary Table 2). To evaluate the robustness of our findings, we also conducted analyses stratifying by stimulant subtype (Supplementary Table 3, 5-6) and event (Supplementary Table 4-6). We further conducted subgroup analyses to assess if potential protective effects of bupropion were sustained in patients who were not receiving OUD medications during insurance enrollment (Supplementary Table 3, 4-6). To test the specificity of our findings, we evaluated associations of bupropion, SSRIs, and OUD medications with drug-related poisonings non-specific to stimulants (Supplementary Table 7). In addition, given previous literature showing efficacy of bupropion and naltrexone extended-release in contributing to negative urine drug screens in methamphetamine use disorder,<sup>12</sup> we evaluated potential interactive effects between bupropion and OUD medications (buprenorphine, naltrexone, and methadone) (Supplementary Table 8). Finally, we conducted secondary analyses by evaluating associations of stimulant-related ED and hospital admissions with mirtazapine treatment days, previously found to be associated with decreased methamphetamine use,<sup>16</sup> as well as proton-pump inhibitors treatment days (negative control), which would not be predicted to have large effects on stimulant-related events (Supplementary Table 9).

Secular time trends were controlled using restricted cubic splines (i.e., mathematical transformation that allows for smooth, flexible but non-linear association between time and risk for outcome). Time-invariant variables did not require adjustment, as case-crossover design permits individuals to serve as their own controls

## Supplementary Figure 1: Derivation of the analytic sample for sensitivity analyses

304,676 individuals aged 12 and older with a diagnosis of OUD in the MarketScan Databases who had prescription drug coverage and at least one opioid use disorder claim falling during period of enrollment



51,084 individuals who had **any** stimulant-related events, encompassing 30,584,584 person days in the 1 year before and after index stimulant-related event (**Model 1, Figure 1**).

- 17,010 individuals with any stimulant-related fall, injury, or poisoning, spanning 10,519,771 person-days in the 1 year before and after index fall, injury, or poisoning (**Model 1, Supplementary Table 4**)
  - 12,077 individuals spanning 7,428,702 person-days in the 1 year before and after index cocaine-related fall, injury, or poisoning (**Model 1, Supplementary Table 5**)
  - 6,148 individuals spanning 3,850,004 person-days in the 1 year before and after index amphetamine-related fall, injury, or poisoning (**Model 1, Supplementary Table 6**)
- 14,700 individuals with stimulant-related psychotic events, spanning 9,020,250 person-days in the 1 year before and after index psychotic event (**Model 2, Supplementary Table 4**)
  - 10,290 individuals spanning 6,301,669 person-day in the 1 year before and after index cocaine-related psychotic event (**Model 2, Supplementary Table 5**)
  - 5,714 individuals spanning 3,520,487 person-days in the 1 year before and after index amphetamine-related psychotic event (**Model 2, Supplementary Table 6**)

Excluding 24,936 individuals who received any OUD medication (naltrexone, methadone, buprenorphine).

Excluding 26,164 individuals who never received any OUD medication (naltrexone, methadone, buprenorphine).

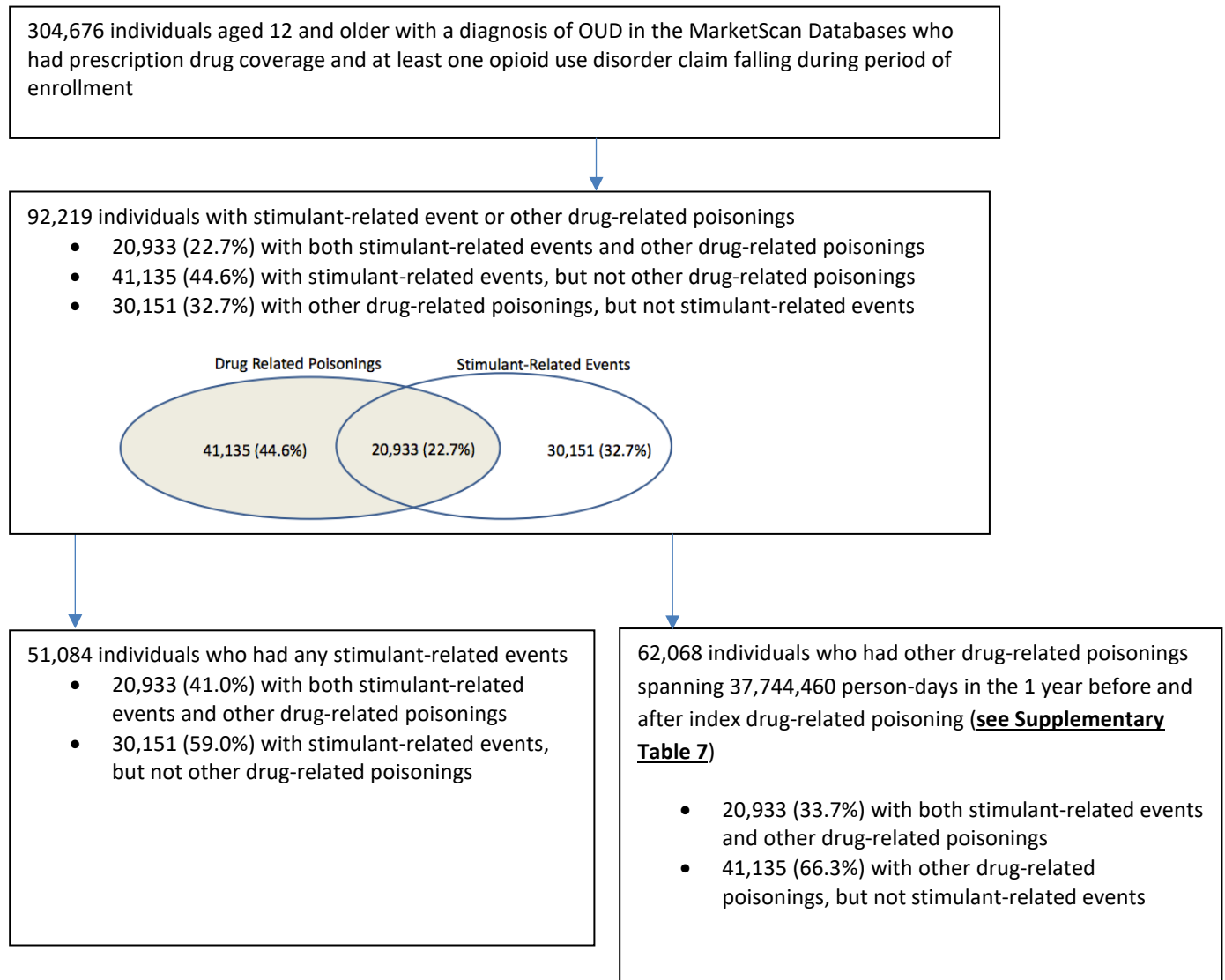
26,148 individuals who did not receive OUD medication during insurance enrollment encompassing 15,489,199 person-days in the 1 year before and after index stimulant-related event (**Model 1, Supplementary Table 3**)

- 9,032 individuals with any stimulant-related fall, injury, or poisoning, spanning 5,560,418 person-days in the 1 year before and after index fall, injury, or poisoning. (**Model 3, Supplementary Table 4**)
  - 6,471 individuals spanning 3,975,866 person-days in the 1 year before and after index cocaine-related fall, injury, or poisoning (**Model 3, Supplementary Table 5**)
  - 3,051 individuals spanning 1,972,655 person-days in the 1 year before and after index amphetamine-related fall, injury, or poisoning (**Model 3, Supplementary Table 6**)
- 7,905 individuals with stimulant-related psychotic events, spanning 4,803,990 person-days in the 1 year before and after index psychotic event (**Model 4, Supplementary Table 4**)
  - 5,630 individuals spanning 3,423,119 person-day in the 1 year before and after index cocaine-related psychotic event (**Model 4, Supplementary Table 5**)
  - 3,182 individuals spanning 1,805,328 person-days in the 1 year before and after index amphetamine-related psychotic event (**Model 4, Supplementary Table 6**)

24,920 individuals who received OUD medication during insurance enrollment encompassing 15,087,351 person-days in the 1 year before and after index amphetamine related event (**Model 4, Supplementary Table 3**)

- 8,199 individuals with any stimulant-related fall, injury, or poisoning, spanning 4,956,552 person-days in the 1 year before and after index fall, injury, or poisoning. (**Model 5, Supplementary Table 4**)
  - 5,603 individuals spanning 3,450,712 person-days in the 1 year before and after index cocaine-related fall, injury, or poisoning (**Model 5, Supplementary Table 5**)
  - 2,965 individuals spanning 1,876,510 person-days in the 1 year before and after index amphetamine-related fall, injury, or poisoning (**Model 5, Supplementary Table 6**)
- 6,793 individuals with stimulant-related psychotic events, spanning 4,214,038 person-days in the 1 year before and after index psychotic event (**Model 6, Supplementary Table 4**)
  - 4,658 individuals spanning 2,876,899 person-day in the 1 year before and after index cocaine-related psychotic event (**Model 6, Supplementary Table 5**)
  - 2,743 individuals spanning 1,714,446 person-days in the 1 year before and after index amphetamine-related psychotic event (**Model 6, Supplementary Table 6**)

**Supplementary Figure 2:** Derivation of the final analytic sample for main outcomes (Figure 1, Supplementary Tables 2-4) as well as secondary analysis (Supplementary Table 7)



**Supplementary Table 1:** Diagnosis Codes for Stimulant-Related Events and Drug-Related Poisonings

Diagnosis	ICD-9/-10-CM diagnosis codes
Any Stimulant Related Admission	'F14' 'F15' 'T40.5' 'T43.6' '305.6' '304.2' '304.4' '305.7' '969.7' '970.0' '970.1' '970.9' '970.81' '970.89'
Any Cocaine Related Admission	'F14' 'T40.5' '305.6' '304.2' '970.81'
Any Amphetamine Related Admission	'F15' '305.7' '304.4' '969.7' '970.0' '970.1' '970.9' 'T43.6' '970.89'
Any Admission for Stimulant-Related Psychotic Event	Any of the following: ('F14' 'F15' 'T40.5' 'T43.6' '305.6' '304.2' '304.4' '305.7' '969.7' '970.0' '970.1' '970.9' '970.81' '970.89' )  AND  Any of the following: ('F20' 'F22' 'F23' 'F24' 'F25' 'F28' 'F29' '292' '293' '295' '297' '298' 'F302' 'F312' 'F315' 'F323' 'F333' '296.04' '296.14' '296.24' '296.34' '296.44' '296.54' '296.64')
Any Admission for Stimulant-Related Fall, Injury, or Poisoning	Any of the following: ('F14' 'F15' 'T40.5' 'T43.6' '305.6' '304.2' '304.4' '305.7' '969.7' '970.0' '970.1' '970.9' '970.81' '970.89' )  AND  Any of the following: ('V01' 'V02' 'V03' 'V04' 'V05' 'V06' 'V10' 'V11' 'V12' 'V13' 'V14' 'V15' 'V16' 'V17' 'V18' 'V20' 'V21' 'V22' 'V23' 'V24' 'V25' 'V26' 'V27' 'V28' 'V29' 'V30' 'V31' 'V32' 'V33' 'V34' 'V35' 'V36' 'V37' 'V38' 'V39' 'V40' 'V41' 'V42' 'V43' 'V44' 'V45' 'V46' 'V47' 'V48' 'V49' 'V50' 'V51' 'V52' 'V53' 'V54' 'V55' 'V56' 'V57' 'V58' 'V59' 'V60' 'V61' 'V62' 'V63' 'V64' 'V65' 'V66' 'V67' 'V68' 'V69' 'V70' 'V71' 'V72' 'V73' 'V74' 'V75' 'V76' 'V77' 'V78' 'V79' 'V80' 'V81' 'V82' 'V83' 'V84' 'V85' 'V86' 'V87' 'V88' 'V90' 'V91' 'V92' 'V93' 'V94' 'V95' 'V96' 'V97' 'W00' 'W01' 'W02' 'W03' 'W04' 'W05' 'W06' 'W07' 'W08' 'W09' 'W10' 'W11' 'W12' 'W13' 'W14' 'W15' 'W16' 'W17' 'W18' 'W19' 'W24' 'W25' 'W26' 'W27' 'W28' 'W29' 'W30' 'W31' 'W32' 'W33' 'W34' 'W45' 'W65' 'W66' 'W67' 'W68' 'W69' 'W70' 'W73' 'W74' 'W78' 'W79' 'X00' 'X01' 'X02' 'X03' 'X04' 'X05' 'X06' 'X08' 'X09' 'X31' 'X40' 'X41' 'X42' 'X43' 'X44' 'X46' 'X47' 'X48' 'X49' 'X60' 'X61' 'X62' 'X63' 'X64' 'X66' 'X67' 'X68' 'X69' 'X70' 'X71' 'X72' 'X73' 'X74' 'X75' 'X76' 'X77' 'X78' 'X79' 'X80' 'X81' 'X82' 'X83' 'X84' 'X85' 'X86' 'X87' 'X88' 'X89' 'X90' 'X91' 'X92' 'X93' 'X94' 'X95' 'X96' 'X97' 'X98' 'X99' 'Y00' 'Y01' 'Y02' 'Y03' 'Y04' 'Y05' 'Y06' 'Y07' 'Y08' 'Y09' 'Y09.0' 'Y09.1' 'Y09.2' 'Y09.3' 'Y09.9' 'Y19.0' 'Y19.1' 'Y19.2' 'Y19.3' 'Y19.4' 'Y19.5' 'Y19.6' 'Y19.8' 'Y19.9' 'Y89.0' 'Y89.1' 'Y89.2' 'Y89.3' 'Y89.9' 'Y87.0' 'Y87.1' 'E800' 'E801' 'E802' 'E803' 'E804' 'E805' 'E806' 'E807' 'E810' 'E811' 'E812' 'E813' 'E814' 'E815' 'E816' 'E817' 'E818' 'E819' 'E820' 'E821' 'E822' 'E823' 'E824' 'E825' 'E826' 'E827' 'E828' 'E829' 'E830' 'E831' 'E832' 'E833' 'E834' 'E835' 'E836' 'E837' 'E838' 'E840' 'E841' 'E842' 'E843' 'E844' 'E845' 'E848' 'E850' 'E851' 'E852' 'E853' 'E854' 'E855' 'E856' 'E857' 'E858' 'E860' 'E861' 'E862' 'E863' 'E864' 'E865' 'E866' 'E867' 'E868' 'E869' 'E880' 'E881' 'E882' 'E883' 'E884' 'E885' 'E886' 'E887' 'E888' 'E890' 'E891' 'E892' 'E893' 'E894' 'E895' 'E896' 'E897' 'E898' 'E899' 'E901' 'E910' 'E911' 'E917' 'E918' 'E919' 'E920' 'E922' 'E950' 'E951' 'E952' 'E953' 'E954' 'E955' 'E956' 'E957' 'E958' 'E959' 'E960' 'E961' 'E962' 'E963' 'E964' 'E965' 'E966' 'E967' 'E968' 'E969' 'E924.1')
Any Admission for Cocaine-Related Psychotic Event	Any of the following: ('F14' 'T40.5' '305.6' '304.2' '970.81' )  AND  Any of the following: ('F20' 'F22' 'F23' 'F24' 'F25' 'F28' 'F29' '292' '293' '295' '297' '298' 'F302' 'F312' 'F315' 'F323' 'F333' '296.04' '296.14' '296.24' '296.34' '296.44' '296.54' '296.64')
Any Admission for Cocaine-Related Fall, Injury, or Poisoning	Any of the following: ('F14' 'T40.5' '305.6' '304.2' '970.81' )  AND  Any of the following: ('V01' 'V02' 'V03' 'V04' 'V05' 'V06' 'V10' 'V11' 'V12' 'V13' 'V14' 'V15' 'V16' 'V17' 'V18' 'V20' 'V21' 'V22' 'V23' 'V24' 'V25' 'V26' 'V27' 'V28' 'V29' 'V30' 'V31' 'V32' 'V33' 'V34' 'V35' 'V36' 'V37' 'V38' 'V39' 'V40' 'V41' 'V42' 'V43' 'V44' 'V45' 'V46' 'V47' 'V48' 'V49' 'V50' 'V51' 'V52' 'V53' 'V54' 'V55' 'V56' 'V57' 'V58' 'V59' 'V60' 'V61' 'V62' 'V63' 'V64' 'V65' 'V66' 'V67' 'V68' 'V69' 'V70' 'V71' 'V72' 'V73' 'V74' 'V75' 'V76' 'V77' 'V78' 'V79' 'V80' 'V81' 'V82' 'V83' 'V84' 'V85' 'V86' 'V87' 'V88' 'V90' 'V91' 'V92' 'V93' 'V94' 'V95' 'V96' 'V97' 'W00' 'W01' 'W02' 'W03' 'W04' 'W05' 'W06' 'W07' 'W08' 'W09' 'W10' 'W11' 'W12' 'W13' 'W14' 'W15' 'W16' 'W17' 'W18' 'W19' 'W24' 'W25' 'W26' 'W27' 'W28' 'W29' 'W30' 'W31' 'W32' 'W33' 'W34' 'W45' 'W65' 'W66' 'W67' 'W68' 'W69' 'W70' 'W73' 'W74' 'W78' 'W79' 'X00' 'X01' 'X02' 'X03' 'X04' 'X05' 'X06' 'X08' 'X09' 'X31' 'X40' 'X41' 'X42' 'X43' 'X44' 'X46' 'X47' 'X48' 'X49' 'X60' 'X61' 'X62' 'X63' 'X64' 'X66'

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Any Admission for Amphetamine-Related Psychotic Event	Any of the following: ('F15' '305.7' '304.4' '969.7' '970.0' '970.1' '970.9' 'T43.6' '970.89')  AND  Any of the following: ('F20' 'F22' 'F23' 'F24' 'F25' 'F28' 'F29' '292' '293' '295' '297' '298' 'F302' 'F312' 'F315' 'F323' 'F333' '296.04' '296.14' '296.24' '296.34' '296.44' '296.54' '296.64')
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Any Admission for Drug-Related Poisonings and Accidents (not specific to stimulant-related events)	'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'

**Supplementary Table 2:** Odds of hospitalization or emergency room admission for any stimulant-related events associated with medication treatment days, stratified by sex, age, and year of insurance enrollment

	Female			Male		
	n=20,440 individuals			n=6,984 individuals		
	OR	95% CI		OR	95% CI	
Bupropion	0.77	0.7	0.85	0.77	0.71	0.84
SSRIs (active comparator)	0.89	0.85	0.94	0.9	0.85	0.95
Buprenorphine	0.66	0.61	0.71	0.69	0.65	0.74
Methadone	0.55	0.47	0.65	0.67	0.52	0.86
Naltrexone	0.65	0.58	0.72	0.65	0.59	0.72
P<.0001 for all						
	Age under 30			Age 30+		
	n=27,669 individuals			n=23,415 individuals		
	OR	95% CI		OR	95% CI	
Bupropion	0.75	0.68	0.82	0.8	0.73	0.88
SSRIs (active comparator)	0.88	0.84	0.93	0.91	0.86	0.96
Buprenorphine	0.73	0.69	0.77	0.59	0.55	0.64
Methadone	0.63	0.5	0.79	0.56	0.47	0.67
Naltrexone	0.66	0.61	0.72	0.61	0.53	0.7
P<.0001 for all						
	Years 2012-2015			Years 2006-2011		
	n=23,337 individuals			n= 27,747 individuals		
	OR	95% CI		OR	95% CI	
Bupropion	0.84	0.75	0.93	0.74	0.68	0.8
SSRIs(active comparator)	0.88	0.83	0.94	0.9	0.86	0.94
Buprenorphine	0.65	0.6	0.7	0.69	0.65	0.73
Methadone	0.6	0.51	0.7	0.54	0.4	0.72
Naltrexone	0.64	0.57	0.71	0.65	0.59	0.72
P<.0001 for all						



**Supplementary Table 3:** Odds of hospitalization or emergency room admission for any stimulant-related events associated with medication treatment days, stratified by stimulant type and OUD subpopulation

	Effect	Any Stimulant-Related (Cocaine or Amphetamines) Admissions N=51,084	Subtypes of Stimulant-Related Events								
			Any Cocaine-Related Admissions n= 35,912 individuals				Any Amphetamine-Related Admissions n= 21,674 individuals				
			Odds Ratio	95% CI			Odds Ratio	95% CI			Odds Ratio
Patients with OUD Not Receiving OUD Medication During Insurance Enrollment n= 26,148 individuals		Model 1 15,489,199 person days			Model 2 10,878,229 person-days			Model 3 6,483,459 person-days			
	Bupropion Days	0.75	0.67	0.84	0.74	0.64	0.85	0.73	0.62	0.85	
	SSRI Days (active comparator)	0.91	0.86	0.96	0.91	0.84	0.98	0.88	0.81	0.95	
Patients with OUD Receiving OUD Medication During Insurance Enrollment, n=24,920 individuals		Model 4 15,087,351 person days			Model 5 10,576,480 person-days			Model 6 6,521,236 person-days			
	Bupropion Days	0.78	0.72	0.85	0.78	0.71	0.87	0.79	0.70	0.88	
	SSRI Days (active comparator)	0.89	0.85	0.93	0.89	0.84	0.94	0.89	0.83	0.95	
	Buprenorphine Days	0.68	0.64	0.71	0.64	0.60	0.67	0.76	0.70	0.82	
	Methadone Days	0.59	0.51	0.67	0.58	0.50	0.68	0.62	0.47	0.81	
	Naltrexone (PO, ER) Days	0.64	0.60	0.69	0.67	0.61	0.74	0.59	0.53	0.65	

P<.0001 for all

Abbreviations: SSRI (selective serotonin reuptake inhibitors), PO (oral), ER (extended-release)

**Supplementary Table 4:** Odds of hospitalization or emergency room admission for any stimulant-related events associated with medication treatment days, stratified by event- type

		Subtypes of Stimulant-Related Admissions					
		Admission for Any Stimulant-Related (Cocaine + Amphetamines) Falls or Injuries and Poisonings			Admission for Any Stimulant-Related (Cocaine + Amphetamines) Psychotic Events		
	Effect	Odds Ratio	95% CI		Odds Ratio	95% CI	
All Patients with OUD, n= 51,084 individuals		<b>(Model 1)</b> 10,519,771 person-days			<b>(Model 2)</b> 9,020,250 person-days		
	Bupropion Days	0.77	0.68	0.87	0.73	0.64	0.84
	SSRI Days (active comparator)	0.87	0.81	0.93	0.80	0.74	0.86
	Buprenorphine Days	0.72	0.66	0.79	0.48	0.44	0.54
	Methadone Days	0.59	0.46	0.76	0.26	0.18	0.37
	Naltrexone (PO, ER) Days	0.71	0.61	0.83	0.44	0.37	0.53
Patients with OUD Not Receiving OUD Medication During Insurance Enrollment, n= 26,148 individuals		<b>(Model 3)</b> 5,560,418 person days			<b>(Model 4)</b> 4,803,990 person-days		
	Bupropion Days	0.75	0.62	0.90	0.63	0.51	0.79
	SSRI Days (active comparator)	0.83	0.75	0.92	0.80	0.72	0.89
Patients with OUD Receiving OUD Medication During Insurance Enrollment, n=24,920 individuals		<b>(Model 5)</b> 4,956,552 person-days			<b>(Model 6)</b> 4,214,038 person-days		
	Bupropion Days	0.78	0.67	0.92	0.80	0.67	0.94
	SSRI Days (active comparator)	0.89	0.82	0.97	0.79	0.72	0.87
	Buprenorphine Days	0.73	0.66	0.80	0.49	0.44	0.54
	Methadone Days	0.60	0.46	0.77	0.27	0.19	0.38
	Naltrexone (PO, ER) Days	0.70	0.60	0.83	0.44	0.37	0.53

P<.0001 for all

Abbreviations: SSRI (selective serotonin reuptake inhibitors), Nal PO (naltrexone Oral), Nal ER (naltrexone extended-release)

**Supplementary Table 5:** Odds of cocaine-related hospitalization or emergency room admission associated with medication treatment days, stratified by event-type

		Any Cocaine-Related Falls or Injuries and Poisonings			Any Cocaine-Related Psychotic Events		
	Effect	Odds Ratio      95% CI			Odds Ratio      95% CI		
All Patients with OUD, n= 35,912 individuals		<b>(Model 1)</b> 7,428,702 person-days			<b>(Model 2)</b> 6,301,669 person-days		
	Bupropion Days	0.77	0.66	0.90	0.72	0.60	0.85
	SSRI Days (active comparator)	0.88	0.81	0.95	0.80	0.73	0.87
	Buprenorphine Days	0.68	0.60	0.76	0.44	0.39	0.50
	Methadone Days	0.56	0.42	0.74	0.19	0.12	0.29
	Naltrexone (PO, ER) Days	0.77	0.63	0.94	0.48	0.38	0.61
Patients with OUD Not Receiving OUD Medication During Insurance Enrollment, N=18,362 individuals		<b>(Model 3)</b> 3,975,866 person-days			<b>(Model 4)</b> 3,423,119 person-days		
	Bupropion Days	0.67	0.52	0.87	0.60	0.45	0.80
	SSRI Days (active comparator)						
		0.84	0.74	0.95	0.81	0.70	0.93
Patients with OUD Receiving OUD Medication During Insurance Enrollment, n= 17,937 individuals		<b>(Model 5)</b> 3,450,712 person-days			<b>(Model 6)</b> 2,876,899 person-days		
	Bupropion Days	0.83	0.68	1.01	0.79	0.64	0.98
	SSRI Days (active comparator)	0.90	0.81	1.00	0.78	0.69	0.88
	Buprenorphine Days	0.68	0.61	0.77	0.44	0.39	0.50
	Methadone Days	0.56	0.43	0.75	0.20	0.13	0.31
	Naltrexone (PO, ER) Days	0.77	0.63	0.94	0.49	0.39	0.61

Abbreviations: SSRI (selective serotonin reuptake inhibitors), Nal PO (naltrexone Oral), Nal ER (naltrexone extended-release)

**Supplementary Table 6:** Odds of amphetamine-related hospitalization or emergency room admission associated with medication treatment days, stratified by event- type

	Effect	Any Amphetamine-Related Falls or Injuries and Poisonings			Any Amphetamine-Related Psychotic Events		
		Odds Ratio	95% CI		Odds Ratio	95% CI	
All Patients with OUD, n= 21,674 individuals		<b>(Model 1)</b> 3,850,004 person-days			<b>(Model 2)</b> 3,520,487 person-days		
	Bupropion Days	0.78	0.65	0.94	0.71	0.58	0.86
	SSRI Days (active comparator)	0.84	0.76	0.93	0.79	0.71	0.87
	Buprenorphine Days	0.81	0.69	0.95	0.58	0.50	0.68
	Methadone Days	0.69	0.41	1.17	0.46	0.25	0.82
	Naltrexone (PO, ER) Days	0.57	0.45	0.74	0.37	0.28	0.48
Patients with OUD Not Receiving OUD Medication During Insurance Enrollment, n= 10,950 individuals		<b>(Model 3)</b> 1,972,655 person-days			<b>(Model 4)</b> 1,805,328 person-days		
	Bupropion Days	0.80	0.61	1.05	0.68	0.50	0.93
	SSRI Days (active comparator)						
		0.78	0.67	0.91	0.76	0.65	0.89
Patients with OUD Receiving OUD Medication During Insurance Enrollment, n=10,959 individuals		<b>(Model 5)</b> 1,876,510 person-days			<b>(Model 6)</b> 1,714,446 person-days		
	Bupropion Days	0.76	0.59	0.98	0.73	0.57	0.94
	SSRI Days (active comparator)	0.89	0.77	1.02	0.80	0.70	0.92
	Buprenorphine Days	0.81	0.69	0.96	0.58	0.50	0.68
	Methadone Days	0.69	0.41	1.17	0.46	0.25	0.82
	Naltrexone (PO, ER) Days	0.56	0.44	0.73	0.36	0.28	0.48

Abbreviations: SSRI (selective serotonin reuptake inhibitors), Nal PO (naltrexone Oral), Nal ER (naltrexone extended-release)

**Supplementary Table 7:** Odds of hospitalization or emergency room admission for drug-related poisonings (non-specific to stimulant-related events)

Admission for All Drug-Related Poisonings,  
n= 62,068 individuals, 37,744,460 person-days

<u>Effect</u>	<u>Point Estimate</u>	<u>95% Confidence Intervals</u>	
Bupropion Days	1.01	0.94	1.07
SSRI Days (active comparator)	0.99	0.96	1.03
Buprenorphine Days	0.62	0.59	0.66
Methadone Days	0.48	0.41	0.55

Abbreviations: SSRI (selective serotonin reuptake inhibitors), Nal PO (naltrexone Oral), Nal ER (naltrexone extended-release)

**Supplementary Table 8:** Analysis of Interactions - Odds of any cocaine- or amphetamine-related hospitalization or emergency room admission associated with medication treatment days, among all Patients with OUD (n=51,084 individuals)

		Any Stimulant-Related (Cocaine + Amphetamines) Admissions 15,087,351 person days			Any Cocaine-Related Admissions, 10,576,480 person-days			Any Amphetamine-Related Admissions 6,521,236 person-days		
<u>Effect</u>		<u>Beta</u>	<u>Standard Error</u>	<u>p-value</u>	<u>Beta</u>	<u>Standard Error</u>	<u>p-value</u>	<u>Beta</u>	<u>Standard Error</u>	<u>p-value</u>
Nal (PO or ER) and Bupro Interaction	Bupro days	-0.26	0.03	<.0001	-0.26	0.04	<.0001	-0.28	0.05	<.0001
	Nal (PO,ER)*Bupro	0.04	0.12	0.76	0.00	0.15	0.99	0.19	0.16	0.24
	SSRI days (active comparator)	-0.11	0.02	<.0001	-0.11	0.02	<.0001	-0.12	0.03	<.0001
	Bupren days	-0.39	0.02	<.0001	-0.46	0.03	<.0001	-0.28	0.04	<.0001
	Methadone days	-0.53	0.07	<.0001	-0.55	0.08	<.0001	-0.47	0.14	0.00
	Nal (PO, ER) Days	-0.44	0.04	<.0001	-0.39	0.05	<.0001	-0.55	0.06	<.0001
Methadone and Bupro Interaction	Bupro days	-0.26	0.03	<.0001	-0.26	0.04	<.0001	-0.27	0.05	<.0001
	Methadone*Bupro	0.11	0.48	0.81	-0.39	0.58	0.51	0.56	0.81	0.49
	SSRI days (active comparator)	-0.11	0.02	<.0001	-0.11	0.02	<.0001	-0.12	0.03	<.0001
	Bupren days	-0.39	0.02	<.0001	-0.46	0.03	<.0001	-0.28	0.04	<.0001
	Methadone days	-0.53	0.07	<.0001	-0.55	0.08	<.0001	-0.48	0.14	0.00
	Nal (PO, ER) Days	-0.44	0.04	<.0001	-0.39	0.05	<.0001	-0.52	0.05	<.0001
Bupren and Bupro Interaction	Bupro days	-0.27	0.03	<.0001	-0.27	0.04	<.0001	-0.30	0.05	<.0001
	Bupren*Bupro	0.14	0.10	0.18	0.09	0.13	0.50	0.34	0.14	0.01
	SSRI days (active comparator)	-0.11	0.02	<.0001	-0.11	0.02	<.0001	-0.12	0.03	<.0001
	Bupren days	-0.40	0.03	<.0001	-0.46	0.03	<.0001	-0.29	0.04	<.0001
	Methadone days	-0.53	0.07	<.0001	-0.55	0.08	<.0001	-0.47	0.14	0.00
	Nal (PO, ER) Days	-0.44	0.04	<.0001	-0.39	0.05	<.0001	-0.52	0.05	<.0001

Abbreviations: SSRI (selective serotonin reuptake inhibitors), Bupro (bupropion), Bupren (buprenorphine), Meth (methadone), Nal PO (naltrexone Oral), Nal ER (naltrexone extended-release)

**Supplementary Table 9:** Sensitivity Analyses-Odds of stimulant-related hospitalization or emergency room admission, controlling for mirtazapine (active comparator) and proton pump inhibitors (negative control)

	Any Stimulant-Related (Cocaine + Amphetamines) Events 30,567,174 person days			Any Cocaine-Related Events, 21,447,716 person-days			Any Amphetamine-Related Events 13,001,584 person-days		
<u>Effect</u>	<u>Point Estimate</u>	<u>95% CI</u>		<u>Point Estimate</u>	<u>95% CI</u>		<u>Point Estimate</u>	<u>95% CI</u>	
Bupro days	0.77	0.72	0.82	0.76	0.70	0.83	0.76	0.70	0.83
Bupren days	0.67	0.64	0.70	0.75	0.70	0.81	0.64	0.60	0.67
Methadone days	0.57	0.49	0.65	0.62	0.47	0.81	0.55	0.47	0.64
Nal (PO,ER) Days	0.65	0.60	0.70	0.59	0.53	0.66	0.68	0.62	0.74
Mirtazapine days (active comparator)	0.90	0.84	0.98	0.84	0.75	0.93	0.88	0.80	0.97
PPI days (negative control)	0.88	0.82	0.94	0.87	0.78	0.97	0.89	0.82	0.96

Abbreviations: Bupro (bupropion), Bupren (buprenorphine), Nal PO (naltrexone Oral), Nal ER (naltrexone extended-release) , PPI (proton pump inhibitor)