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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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ABSTRACT

Background: Stimulant use has substantially increased among people with opioid use disorder (OUD) and is associated with worse treatment outcomes. This study's objective was to compare risk of stimulant-related emergency department (ED) and hospital admissions associated with exposure to bupropion, OUD medication (buprenorphine, naltrexone, and methadone), and selective serotonin reuptake inhibitors (SSRIs; active comparator) relative to days without active prescriptions for medication.

Methods: This recurrent-event, case-crossover study used insurance claims from 51,084 individuals with OUD enrolled in the IBM MarketScan (2006–2016) Databases who had at least 1 stimulant-related ED or hospital admission. Conditional logistic regression models estimated the risk of admissions between days without active prescriptions and days with prescriptions for bupropion, OUD medication, and SSRIs. Secondary analyses were conducted by stimulant subtype (cocaine; amphetamine) and event subtype (falls, injuries, or poisonings; psychotic events).

Results: Compared to days without active prescriptions, days with bupropion treatment were associated with decreased odds of stimulant-related ED or hospital admissions (odds ratio [OR] = 0.77; 95% confidence interval [CI], 0.72–0.82) Among OUD medications, we observed strong protective associations with decreased admissions for buprenorphine (OR = 0.67; 95% CI, 0.64–0.71), naltrexone (OR = 0.65; 95% CI, 0.60–0.70), and methadone (OR = 0.59; 95% CI, 0.51–0.67). The SSRI active comparator group was associated with a small protective association with decreased admissions (OR = 0.90; 95% CI, 0.86–0.93). These effects were sustained in secondary analyses stratifying by stimulant and event subtype.

Conclusions: Bupropion and OUD medication, including both naltrexone and opioid agonists, are associated with fewer stimulant-related ED or hospital admissions in patients with OUD. Bupropion may show promise as adjunctive therapy targeting stimulant-specific poisoning risk.

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Stimulant use is an increasingly common cause of morbidity and mortality in individuals with opioid use disorder (OUD). From 2011 to 2017, amphetamine use nearly doubled from 19% to 34% among people entering OUD treatment programs.[1] Large increases have also been observed for cocaine and opioid co-use.[2] Patients with OUD and co-occurring cocaine and amphetamine use bear worse substance use treatment outcomes[3–7] and suffer from elevated risk of accidents and psychotic episodes.[8–11] Unlike OUD, there are no US Food and Drug Administration–approved medications for the treatment of stimulant use disorder.

Recently, bupropion in combination with naltrexone has emerged as a potential treatment for methamphetamine use disorder without comorbid opioid use,[12] such that individuals randomized to bupropion and naltrexone showed reductions in methamphetamine use confirmed by urine drug screens. It is unclear whether these findings can be generalized to patients with OUD and co-occurring stimulant use. As naltrexone may precipitate withdrawal in people actively using opioids, it is important to investigate the effectiveness of other OUD medications in improving stimulant-related outcomes in patients with OUD, especially since opioid agonist treatments have shown some promise in protecting against stimulant-related adverse events.[13–15] Among patients with OUD who have stimulant misuse, it remains unknown whether bupropion, given its unique stimulant-like mechanism of action, would have a superior protective effect against stimulant use than other antidepressants that may modulate the effects of amphetamines, such as SSRIs and mirtazapine,[16] for which the evidence base for treatment of methamphetamine use remains inconclusive.[17]

The objective of this study is to test the hypothesis that bupropion and OUD medications (buprenorphine, naltrexone, and methadone) are associated with decreased stimulant-related emergency department (ED) admissions and hospitalizations among people with OUD who had at least 1 such admission. We used pharmaceutical claims to analyze acute stimulant-related ED or hospital admissions associated with days

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Clinical Points

- It is unknown if the recently demonstrated protective effect of bupropion and naltrexone in methamphetamine use disorder holds true in patients with opioid use disorder (OUD) and co-occurring stimulant misuse.
- Bupropion and opioid agonist medication may hold promise in the treatment of problematic stimulant use in patients with OUD, especially in individuals actively using opioids who may not tolerate naltrexone.

of bupropion, selective serotonin reuptake inhibitors (SSRIs, active comparator), and OUD medication use in comparison to days without medication receipt, with analyses stratified by stimulant (cocaine; amphetamine) and admission subtype (falls, injuries, or poisonings; psychotic events).

METHODS

Study Design

We conducted a repeated-event, within-person, case-crossover study using the IBM® MarketScan® Commercial and Multi-State Medicaid Databases. Specifically, we used the approach of Allison and Christakis,[18] who advocate employing a large number of consecutive control periods in a conditional logistic model, similar to a stratified Cox regression, rather than conventional case-crossover designs that utilize a discrete number of control days. The use of a repeatable outcome event, as opposed to a fatal event, allows incorporation of time controls into the models.[18] Our objective was to compare the risk of stimulant-related ED or hospital admission in patients with OUD between days when individuals were prescribed bupropion, SSRIs, and OUD medication, in comparison to days without any medication treatment. We also tested for statistical interactions between OUD medication effects and antidepressant effects. The within-person element of our study design used every individual as their own control by comparing medication use at the time of admission with medication use during control periods (without admission); because the comparisons of medication use between admission and non-admission days takes place within same person, the within-person design controls for time-invariant variables such as year of birth, sex, race, and socioeconomic characteristics.

Data Source

Insurance claims were collected from the MarketScan Databases, which encompasses longitudinal claims data representing clinical encounters and filled prescriptions in the US for commercial insurance and Medicaid as previously described.[19,20] Data were available from January 1, 2006, to December 31, 2016. STROBE and RECORD-PE reporting guidelines were followed.

Study Population

Our analytic sample was derived from 304,676 insured patients with OUD in the US, aged 12 to 64 years, who had at least 1 OUD claim during enrollment. This manuscript is a secondary analysis of an existing cohort of individuals with OUD, described in detail previously.[19,20] As illustrated in Figure 1, our use of case-crossover design required analyses to be limited to 51,084 individuals with OUD who had stimulant-related ED or hospital admission (outcome of interest, defined in Supplementary Table 1). We defined the index event as the first admission for each person after initiating OUD treatment. We generated a longitudinal dataset at the day level, encompassing all days of insurance coverage, lasting up to 1 year before and after the index admission, for the mean length of time individuals were observed in our dataset was approximately 2 years. The final dataset thus contained 1 record per day per individual, with person-days constituting the units of observation. We permitted individuals to contribute multiple events as long as they occurred within a maximum of 1 year before and after the index event.

Definition of Exposure

The primary exposure variables were days of pharmacologic treatment by bupropion, SSRIs, or OUD medication (buprenorphine, methadone, naltrexone). To assess whether bupropion suppressed stimulant use via a nonspecific mediating antidepressant action, we selected commonly used SSRIs (sertraline, fluoxetine, escitalopram, and citalopram) as an active comparator to assess whether they had similar associations with decreased stimulant-related events. Mirtazapine was also selected as an active comparator due to its demonstrated protective effects in clinical trials examining methamphetamine use in populations of men who have sex with men (MSM).[16] Commonly used proton pump inhibitors (omeprazole, pantoprazole) were selected as a negative control.

We operationalized exposure to medication as insurance coverage days marked by presence or absence (reference group) of at least 1 filled prescription, with associated NDC (national drug code) and procedure codes for these medications previously described.[19,20] As we assumed each individual initiated medication on the day following the initial prescription date and took it until the last day supplied, the exposure-risk window began on the day immediately after the fill date. We permitted individuals to have gaps of up to 30 days between fill dates before counting them as off medication. Data on covariates such as age, sex, year of enrollment, and insurance status were obtained for the purpose of sample description, with racial/ethnic characteristics only available for Medicaid enrollees.[21]

Definition of Outcomes

The primary outcome was insurance enrollment days marked by stimulant-related ED or hospital admission using *ICD-9*/*10* codes recorded in the insurance claims (Supplementary Table 1). In secondary analyses, stimulant-related admissions were stratified by subtype of stimulant (cocaine-related; amphetamine-related [including methamphetamines]) as well as subtype of event (psychotic

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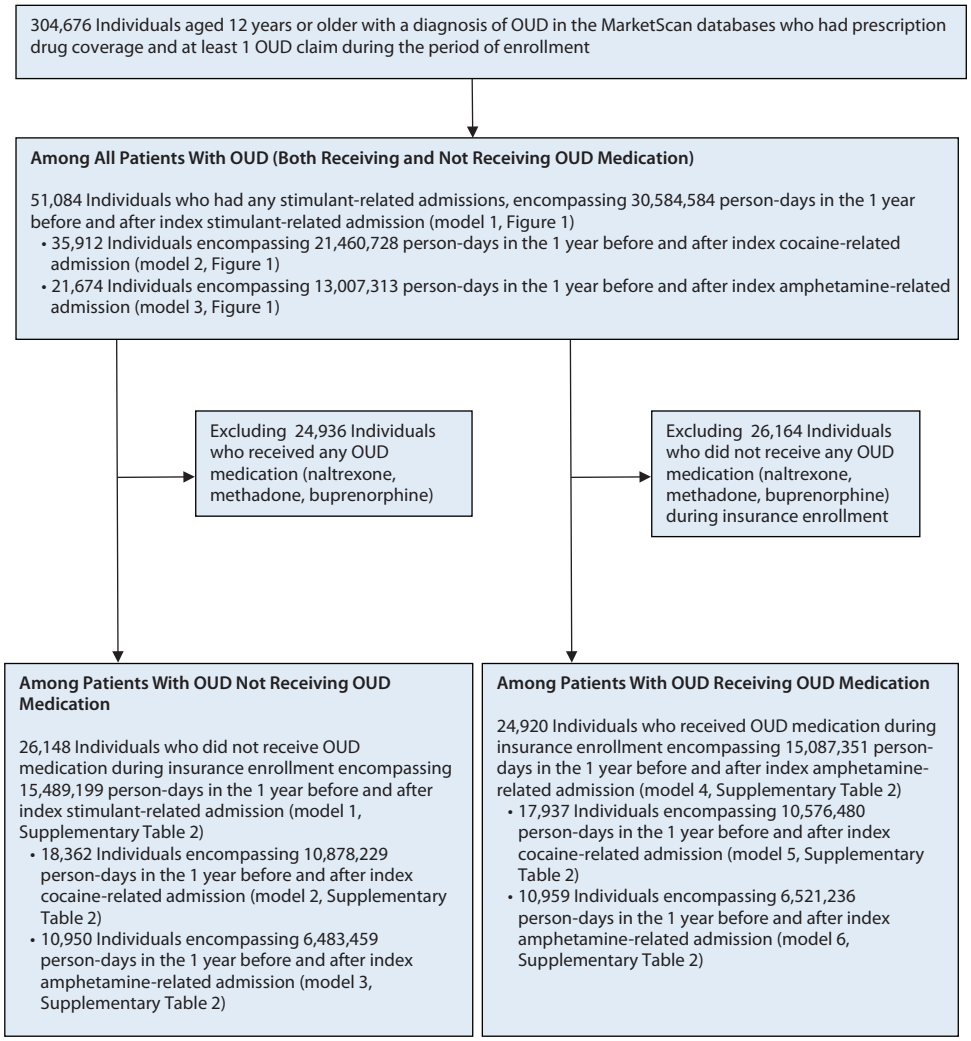
Figure 1. Flowchart for Development of Analytic Sample[a]



[a]Figure 1 illustrates the process by which the final analytic sample was derived. Following application of inclusion and exclusion criteria, there were 51,084 unique patients with OUD. We subsequently restricted the analytic sample to observations within 1 year before and 1 year after index stimulant-related acute event to decrease heterogeneity in observation time. This culminated in a total of 30,584,584 person-days in the study database. Subgroup analyses stratified patients by receipt of OUD medication during insurance enrollment, as well as stimulant subtype (cocaine vs amphetamine).
Abbreviation: OUD = opioid use disorder.

events; falls, injuries, or poisonings), using common adverse events associated with stimulant use (Supplementary Figure 1).[8–11] To assess whether potential protective effects of bupropion were specific to stimulant-related ED or hospital admission, we conducted another secondary analysis using drug-related poisonings nonspecific to stimulants (ie, including but not limited to stimulants) such as nonfatal overdoses involving opioid, alcohol, benzodiazepine, and/or other psychotropic medications; the coding of this variable, per guidelines compiled by Centers for Disease Control and Prevention consensus recommendations for poisoning surveillance, has been previously described.[19]

Statistical Analysis

Details of the statistical methods for conditional logistic regression were similar to those in our previously reported work.[19,20] More specifically, the analysis was limited to observation days spanning up to 1 year before and after index stimulant-related ED or hospital admission. Case days encompassed the index stimulant-related admission and subsequent admissions; control days included all other days within the observation window. For hypothesis testing, odds ratios illustrating associations between stimulant-related admission and medication treatment days were calculated using conditional logistic regression, with each individual identifier ("enrolid") serving as the stratification (conditioning) variable.

As described in detail in the Supplementary Methods, we performed additional analyses to assess robustness of our findings, which include stratifying by event subtype, stimulant subtype, OUD subgroup, age, sex, and year of enrollment, as well as evaluating interactive effects between

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Table 1. Treatment Characteristics at the Individual Participant Level During 1 Year Before and After Index Stimulant-Related Emergency Department Admission or Hospitalization

Characteristic	Total individuals (N = 51,084) n	%
Medication use in the 1 year before and after index event		
Bupropion	6,463	12.7
Mirtazapine, active comparator	4,493	8.8
SSRI, active comparator	16,935	33.2
Proton pump inhibitor, negative comparator	6,298	12.3
Buprenorphine	14,443	28.3
Methadone	2,117	4.1
Naltrexone oral	4,326	8.5
Naltrexone ER	2,243	4.4
Event characteristics		
No. of stimulant-related ED admissions or hospitalizations		
1 Event	39,254	76.8
2 Event	7,826	15.3
3 or More events	4,004	7.8
Diagnoses within 6 months of starting treatment		
Cocaine use disorder	16,737	32.8
Amphetamine use disorder	8,947	17.5
Demographic characteristics		
Insurance		
Private	23,543	46.1
Medicaid	27,541	53.9
Female gender	25,596	50.1
Age	Mean = 30.2 y, median = 28.0 y, SD = 11.5, mode = 23.0 y	
Race among Medicaid enrollees[a]		
White	20,440	74.5
Black	2,932	10.7
Hispanic	449	1.6
Other	3,603	13.1

[a]Data on racial characteristics not provided for private insurance enrollees.
Abbreviations: ED = emergency department, ER = extended-release, SSRI = selective serotonin reuptake inhibitor.

bupropion and OUD medications. For all tests, 2-sided statistical significance levels of .05 were used. Statistical analyses were performed using SAS 9.4.

RESULTS

As shown in Table 1, the final study sample contained 51,084 unique patients with OUD (median 28.0 years; 50.1% female; 75% White among Medicaid recipients; mean observation time, 582.7 days; 30,584,584 person-days of observation time) who had at least 1 stimulant-related ED or hospital admission. Among all individuals with stimulant-related admission, 35,912 individuals had cocaine-related and 21,674 individuals had amphetamine-related admissions (Figure 1). Among persons with stimulant-related admissions, 17,010 individuals had stimulant-related falls, injuries, or poisonings, and 14,700 individuals had psychotic events (Supplementary Figure 2). While 14,443 (28.3%) received buprenorphine in the year before and after the index admission, 2,117 (4.1%) received methadone, 4,326 (8.5%) received naltrexone oral (PO), 2,243 (4.4%) received naltrexone extended-release (ER), and 6,463 (12.7%) received bupropion. For active comparator variables, 16,935 (33.2%) received SSRIs and 4,493 (8.8%) mirtazapine in the year before and after index admission. 6,298 (12.3%) received proton pump inhibitors (negative comparator variable). 32.8% (n = 16,737) had recent claims for cocaine use disorder, and 17.5% (n = 8,947) had claims for amphetamine use disorder in the 6 months preceding or including the start of treatment.

Main Effects

Figure 2 shows odds ratios of stimulant-related ED or hospital admissions associated with days when individuals used bupropion, SSRIs, and OUD medications in comparison to non-medication days. In model 1, among all individuals with OUD, days on which participants were taking bupropion was associated with 23% (OR = 0.77 [95% CI, 0.72–0.82]) reductions in odds of stimulant-related admissions relative to non-medication days; days of SSRI use were associated with 10% (OR = 0.90 [0.86–0.93]) reductions in odds of stimulant-related admissions. Among medications for OUD, days of buprenorphine, methadone, and naltrexone (ER or PO) use were associated with 33% (OR = 0.67 [0.64–0.71]), 41% (OR = 0.59 [0.51–0.67]), and 35% (OR = 0.65 [0.60–0.70]) reductions, respectively, in odds of admissions (model 1, Figure 2). These findings were also robust in subgroup analyses stratifying for sex, age (under 30 years vs 30+ years), and White versus non-White race (Supplementary Table 2). We further evaluated the relationship of bupropion and SSRI treatment days with stimulant-related admissions among patients with OUD who did not receive OUD medication during insurance enrollment (model 1, Supplementary Table 3), finding that days of bupropion treatment were associated with 25% reductions in risk of stimulant-related admissions (OR = 0.75 [0.67–0.84]) relative to non-treatment days, with more modest effects observed for SSRI treatment days (OR = 0.90 [0.86–0.93]).

Subgroup and Interaction Analyses

We repeated analyses across participants of different stimulant subtypes. Model 2 (Figure 2) shows consistently decreased odds of all cocaine-related admissions associated with bupropion (OR = 0.77 [0.71–0.84]), SSRIs (OR = 0.90 [0.86–0.94]), buprenorphine (OR = 0.63 [0.60–0.67]), methadone (OR = 0.58 [0.49–0.67]), and naltrexone (OR = 0.68 [0.62–0.74]) in comparison to days without medication treatment. In addition, model 3 (Figure 2) illustrates consistently decreased odds of all amphetamine-related admissions across all examined medication classes relative to days without medication treatment, with these effects sustained in subgroup analyses stratifying by event subtype (Supplementary Tables 4, 5, and 6).

Additional analyses evaluated associations between OUD medication, bupropion, and SSRI treatment days and drug-related poisonings not specific to stimulants; we found that the associations of bupropion and SSRIs with decreased stimulant-related admissions (Figure 2) did not hold for the broader category of drug-related overdoses and poisonings

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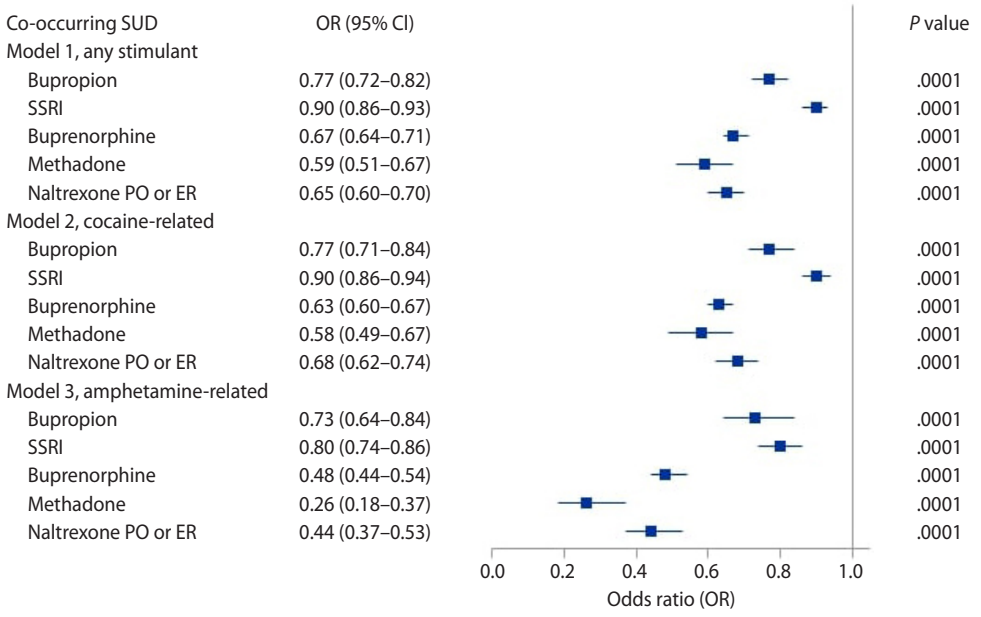
Figure 2. Odds of Stimulant-Related ED and Hospital Admissions Associated With Medication Treatment Days Compared With Nontreatment Days[a]



[a]Figure 2 shows forest plots depicting odds ratios of stimulant-related ED or hospital admissions associated with medication treatment days compared to non-treatment days, stratified for cocaine-related and amphetamine-related admissions. Models adjusted for the effects of each medication together (bupropion, SSRI, buprenorphine, methadone, and naltrexone oral or extended-release) as well as time effects using cubic splines. Model 1 encompasses 30,584,584 person-days of observation among 51,084 individuals with OUD who had at least 1 stimulant-related ED or hospital admission. Model 2 encompasses 21,460,728 person-days among 35,912 individuals with OUD who had at least 1 cocaine-related ED or hospital admission. Model 3 encompasses 13,007,313 person-days among 21,674 individuals with OUD who had at least 1 amphetamine-related ED or hospital admission.

Abbreviations: ED = emergency department, ER = extended-release, OUD = opioid use disorder, PO = oral, SSRI = selective serotonin reuptake inhibitor, SUD = substance use disorder.

that was not restricted to stimulants (Supplementary Table 7). We evaluated the possibility of interaction effects between OUD medications and bupropion, finding no significant interactions observed between bupropion and all OUD medications (Supplementary Table 8) for any stimulant-, cocaine-, or amphetamine-related admissions. Bupropion and all OUD medications showed significantly stronger protective associations with decreased stimulant-related admissions than mirtazapine (active comparator) and proton pump inhibitors (negative control) (Supplementary Table 9).

DISCUSSION

Our findings show that among persons with opioid use disorder, bupropion and OUD medications were associated with decreased risk of stimulant-related ED or hospital admissions. This study illustrates robust associations between bupropion or OUD medication and reductions in both cocaine- and amphetamine-related admissions, spanning psychotic events, falls, injuries, and poisonings. As recent studies[12] have illustrated that bupropion and naltrexone, in combination, are efficacious in reducing amphetamine use, this analysis extends the literature base by evaluating the association of bupropion and OUD medications—including agonist maintenance medications—with stimulant-related admissions among patients with OUD.

To our knowledge, this is the first large-scale demonstration that buprenorphine and methadone may be associated with improved stimulant-related outcomes, suggesting that the benefits of opioid agonist treatment extend beyond solely OUD.[20] Our findings represent hopeful news for patients with OUD and co-occurring stimulant misuse, as naltrexone may precipitate withdrawal in people actively using opioids, thus limiting generalizability of the bupropion and naltrexone combination. Our results suggest that buprenorphine, which has a shorter window of withdrawal prior to initiation, may thus have therapeutic utility for patients with OUD and stimulant use. Buprenorphine treatment in patients with OUD and co-occurring stimulant use has also been found to correlate with reduced cravings and ultimately decreased cocaine and amphetamine use.[7,22,23]

This study also suggests modest improvements in bupropion's potential protective association with decreased stimulant-related admissions over SSRIs and mirtazapine, although all 3 appear to be associated with decreased admissions. Given that patients with OUD and comorbid stimulant use are at risk of increased burden of psychopathology, including psychotic and affective illness,[3,24–27] it is plausible that bupropion is treating underlying psychiatric comorbidity. Interestingly, bupropion also appears to correlate with improved stimulant-related outcomes but not drug-related poisonings in general; this

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may suggest that bupropion's association with decreased stimulant-related admissions is relatively specific to stimulant-related adverse events as opposed to other types of drug overdoses, as bupropion has previously been found to improve dysphoria specifically associated with amphetamine withdrawal via its dopaminergic and noradrenergic activity, which may mitigate cravings and relapse risk in individuals with problematic stimulant use. We also illustrated decreased risk of stimulant-related admissions associated with bupropion treatment days in patients with OUD not receiving OUD medication, further suggesting independent protective effects against stimulant admissions that is not necessarily mediated by OUD medications. In light of these findings, mechanisms for bupropion's efficacy in improving stimulant-related outcomes warrant further investigation. Of note, we illustrated that bupropion and naltrexone exhibit additive but *not* interactive effects in association with decreased stimulant-related admissions. This suggests that any protective effect of bupropion and naltrexone in combination is more reflective of the summation of their individual effects, as opposed to magnified effects produced by these medications taken together.

There are several limitations to consider. First, the temporality of exposure and outcome warrant further investigation. Given that amphetamine use is significantly associated with lower retention in buprenorphine treatment,[7] it is plausible that successful treatment of underlying stimulant use may contribute to better OUD medication concordance. However, stimulant use may also decrease an individual's likelihood to initiate or remain on OUD medication.[7,28] More investigation is ultimately needed to characterize this complex interplay. Second, our results should be interpreted in conjunction with known differences in treatment retention and induction success, as the true practical effectiveness of OUD medications and bupropion may be hindered by treatment discontinuation, which, in turn, may be impacted by the presence of co-occurring stimulant use disorders.[7,28,29] For instance, lower treatment discontinuation has been observed for buprenorphine[30] and methadone[31] treatment than naltrexone in OUD populations. The effectiveness of naltrexone therapy was significantly attenuated by unsuccessful induction in the recent intention-to-treat comparison of buprenorphine and extended-release naltrexone.[32]

Third, our study is limited by measurement error, such that medication coverage does not always reflect actual consumption in the MarketScan data, and insurance claims do not differentiate between different types of amphetamine-related events and amphetamine use disorders. Unmeasured time-varying factors associated with stimulant-related admissions can also introduce confounding, although we mitigated this by introducing calendar time and time from event as covariates and restricting individuals to 2-year observation periods surrounding the index admission in order to reduce heterogeneity in observation time, with bidirectional sampling used to reduce overlap bias resulting from control period selection as functions of event time. A fourth limitation is that we cannot rule out residual confounding from unmeasured time-invariant variables. For instance, a component of bupropion, naltrexone, and buprenorphine's protective association with decreased stimulant-related admissions may stem from engagement with the health care system, evidenced by a small but statistically significant protective effect associated with proton pump inhibitors (negative control).

Fifth and finally, although the data stem from large national samples with long-term follow-up, the study's external validity is limited by an insured, mostly Caucasian population with observed stimulant-related events culminating in hospital or emergency department admission, with data extending only to 2015, prior to the subsequent rise in stimulant use toward the end of the decade. Our results also may not be generalizable to the broader population of people with OUD and stimulant misuse, especially since illicit drug use is not captured in insurance claims, or people with stimulant use disorder without OUD. While there is a high prevalence of problematic methamphetamine use in MSM populations, for which mirtazapine has shown therapeutic promise,[16] our dataset lacked information on sexual behaviors, highlighting the importance of replicating these findings in MSM populations that are understudied and subjected to discrimination and stigma.[33] Amid the crisis of structural racism contributing to disparities in OUD outcomes,[34] data on racial/ethnic characteristics are unfortunately unavailable in the MarketScan Commercial Database,[21] and it is imperative that these results are investigated in racially and ethnically diverse populations, for which indirect estimation methods of analysis have shown promise.[35,36]

Despite these limitations, our study was strengthened by its repeated-event, case-crossover design and is one of the first pharmacoepidemiologic analyses of treatment for stimulant-related admissions in patients with OUD. Overall, our results support OUD medications as first-line treatment for persons with OUD and co-occurring stimulant use as these medications demonstrate protective associations with decreased stimulant-specific and all-cause drug-related poisonings. Bupropion may show promise as adjunctive therapy targeting stimulant-specific poisoning risk; however, further research is needed to expand the evidence base for this study's findings.

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Author contributions: Drs Xu and Grucza are guarantors and take full responsibility for the content of the manuscript, including data and analysis. Drs Xu, Bierut, and Grucza and Mr Presnall contributed to conception and design. Drs Xu and Grucza and Mr Presnall contributed to analysis. Drs Xu, Bierut, Grucza, and Mintz contributed to interpretation. All authors contributed to manuscript preparation. All authors were involved in the critical revision of the manuscript and approved the version submitted.

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Data sharing statement: No additional data available. The authors will provide relevant code on reasonable written request.

Supplementary material: Available at PSYCHIATRIST.COM

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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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List of Supplementary Material for the article

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10. **Table 7** Odds of Hospitalization or Emergency Room Admission for Drug-Related Poisonings (Non-Specific to Stimulant-Related Events)

11. **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)

12. **Table 9** Sensitivity Analyses: Odds of Stimulant-Related Hospitalization or Emergency Room Admission, Controlling for Mirtazapine (Active Comparator) and Proton Pump Inhibitors (Negative Control)

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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,[12] 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,[16] 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

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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)**

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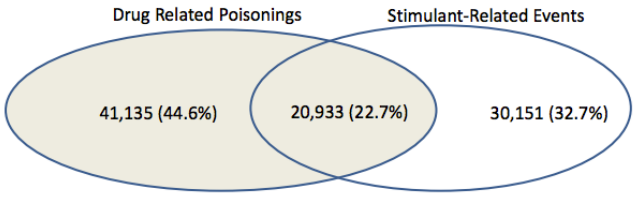
Supplementary Figure 2: Derivation of the final analytic sample for main outcomes (Figure 1, Supplementary Tables 2-4) as well as secondary analysis (Supplementary Table 7)

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

92,219 individuals with stimulant-related event or other drug-related poisonings

- 20,933 (22.7%) with both stimulant-related events and other drug-related poisonings
- 41,135 (44.6%) with stimulant-related events, but not other drug-related poisonings
- 30,151 (32.7%) with other drug-related poisonings, but not stimulant-related events



51,084 individuals who had any stimulant-related events

- 20,933 (41.0%) with both stimulant-related events and other drug-related poisonings
- 30,151 (59.0%) with stimulant-related events, but not other drug-related poisonings

62,068 individuals who had other drug-related poisonings spanning 37,744,460 person-days in the 1 year before and after index drug-related poisoning (**see Supplementary Table 7**)

- 20,933 (33.7%) with both stimulant-related events and other drug-related poisonings
- 41,135 (66.3%) with other drug-related poisonings, but not stimulant-related events

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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' 'V09.0' 'V09.1' 'V09.2' 'V09.3' 'V09.9' 'V19.0' 'V19.1' 'V19.2' 'V19.3' 'V19.4' 'V19.5' 'V19.6' 'V19.8' 'V19.9' 'V89.0' 'V89.1' 'V89.2' 'V89.3' 'V89.9' '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')
Any Admission for Amphetamine-Related Fall, Injury, or Poisoning	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: ('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' 'V09.0' 'V09.1' 'V09.2' 'V09.3' 'V09.9' 'V19.0' 'V19.1' 'V19.2' 'V19.3' 'V19.4' 'V19.5' 'V19.6' 'V19.8' 'V19.9' 'V89.0' 'V89.1' 'V89.2' 'V89.3' 'V89.9' '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 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'

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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						

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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

		Any Stimulant-Related (Cocaine or Amphetamines) Admissions N=51,084			Subtypes of Stimulant-Related Events: Any Cocaine-Related Admissions n= 35,912 individuals			Subtypes of Stimulant-Related Events: Any Amphetamine-Related Admissions n= 21,674 individuals		
	Effect	Odds Ratio	95% CI		Odds Ratio	95% CI		Odds Ratio	95% CI	
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)

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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		**(Model 1)** 10,519,771 person-days			**(Model 2)** 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		**(Model 3)** 5,560,418 person days			**(Model 4)** 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		**(Model 5)** 4,956,552 person-days			**(Model 6)** 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)

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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		**(Model 1)** 7,428,702 person-days			**(Model 2)** 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		**(Model 3)** 3,975,866 person-days			**(Model 4)** 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		**(Model 5)** 3,450,712 person-days			**(Model 6)** 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)

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

		Any Amphetamine-Related Falls or Injuries and Poisonings			Any Amphetamine-Related Psychotic Events		
	Effect	Odds Ratio	95% CI		Odds Ratio	95% CI	
All Patients with OUD, n= 21,674 individuals		**(Model 1)** 3,850,004 person-days			**(Model 2)** 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		**(Model 3)** 1,972,655 person-days			**(Model 4)** 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		**(Model 5)** 1,876,510 person-days			**(Model 6)** 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)

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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

Effect	Point Estimate	95% Confidence Intervals	
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		
	Effect	Beta	Standard Error	p-value	Beta	Standard Error	p-value	Beta	Standard Error	p-value
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)

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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		
Effect	Point Estimate	95% CI		Point Estimate	95% CI		Point Estimate	95% CI	
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)

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