PHARMACOLOGICAL TREATMENTS

Prescription amphetamines in people with opioid use disorder and co-occurring psychostimulant use disorder initiating buprenorphine: an analysis of treatment retention and overdose risk

Vitor Tardelli Vitorstardelli@gmail.com 1,2 Kevin Y Xu,3 Adam Bisaga,4,5 Frances R Levin,4 Thiago M Fidalgo,1 Richard A Grucza6,7

ABSTRACT

Background Attention-deficit and hyperactivity disorder (ADHD) is frequently diagnosed in patients with substance use disorders (SUDs), including opioids. There remains concern about the safety and efficacy of prescription amphetamines (PAs) and their impact on effectiveness of opioid use disorder (OUD) treatment with buprenorphine.

Objectives To assess the effect of PAs on OUD buprenorphine treatment retention and/or SUD-related emergency admission or drug-related poisonings.

Methods We used a retrospective cohort design with a secondary analysis of data from Merative MarketScan Commercial and Multi-State Medicaid Databases from 1 January 2006 to 31 December 2016. Individuals included were aged 12–64 years, had an OUD diagnosis and were prescribed buprenorphine. Our analysis used multivariable Cox regression to evaluate the relationship between PA receipt and time to buprenorphine discontinuation. The second part focused on subsamples of buprenorphine initiators who had either (1) any SUD-related emergency admissions or (2) drug-related poisoning. These outcomes were modelled as a function of PA exposure using conditional logistic regression models as part of a within-person, case-crossover design.

Findings Our sample had 90,269 patients with OUD (mean age 34.2 years (SD=11.3)) who initiated buprenorphine. Being prescribed a PA was associated with improved buprenorphine retention among individuals both with (adjusted HR (aHR) 0.91 (95% CI 0.86 to 0.97)) and without a concurrent psychostimulant use disorder (PSUD) (aHR 0.92 (95% CI 0.90 to 0.93)).

Conclusions PA use was associated with improved buprenorphine retention in people with OUD with and without co-occurring PSUD. The risks of acute SUD-related events and drug-related poisonings associated with PA use did not differ when comparing PA-using days with days without PA use.

Clinical implications Patients with OUD on buprenorphine should receive treatment with a PA when indicated.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prescription amphetamines (PAs) are useful to treat attention-deficit and hyperactivity disorder (ADHD).
⇒ ADHD is a frequent comorbidity for substance use disorders.

WHAT THIS STUDY ADDS

⇒ PAs improve buprenorphine treatment retention in patients with opioid use disorder (OUD).
⇒ PAs do not increase risk of poisoning among patients with OUD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Individuals with OUD should be treated with PAs when necessary.
⇒ PAs may improve OUD-related outcomes.

BACKGROUND

Drug-related poisoning deaths involving psychostimulants have steeply increased over the past decade in the USA, and even more so when concurrently used with illicit synthetic opioids. The concurrent use of psychostimulants and opioids has been increasing over the past decade in countries like the USA and Canada, and the rise in drug-related poisoning deaths involving psychostimulants and opioids has been termed the ‘fourth wave’ of the opioid overdose crisis. There is an increasing presence of synthetic opioids, such as fentanyl and its analogues contaminating street supplies of methamphetamine and cocaine. This puts individuals who seek psychostimulants at a risk of drug-related poisoning when using an adulterated substance, as they may have no prior exposure or tolerance to opioids. A recent study shows that methamphetamine poisoning deaths, with and without concurrent involvement of opioids, have increased steeply over the last decade in the USA. Moreover, simultaneous psychostimulant use disorder (PSUD, including cocaine use disorder (CUD) and methamphetamine use disorder (MUD)) and opioid use disorder (OUD) have become more prevalent over the same period in North America and Australia. Non-prescribed psychostimulants and opioids pose higher risk of drug-related poisoning deaths...
when used together as compared with each drug alone and a recent study has found that using psychostimulants and opioid concurrently poses twice the risk of a fatal overdose compared with using opioids alone. The opioid partial agonist buprenophine is the most common maintenance medication used in treatment of OUD. Patients in treatment for OUD may need prescription stimulant medications for the treatment of attention-deficit and hyperactivity disorder (ADHD), as recent evidence has demonstrated that treating ADHD among patients with OUD may improve retention in treatment and reduce illicit substance use. Moreover, a recent meta-analysis shows that prescription amphetamines (PAs) in particular, are a potentially useful tool to treat PSUD, especially CUD, as it is able to promote abstinence and reduce drug use. Examples of benefits of PA use for individuals with PSUD include increased treatment retention and reduction in all-cause mortality. This represents a challenge for clinicians who should carefully weigh potential risks and benefits of prescription stimulants when treating patients with OUD and/or PSUD.

Despite evidence supporting the efficacy of PAs in treating PSUD (particularly CUD), there remains concern about the safety of PAs in people with OUD with or without co-occurring PSUD. In people without substance use disorders (SUDs), PAs are considered safe for the treatment of ADHD, with an incidence of cardiac side adverse effects similar to methylphenidate. Extended-release formulations of PAs available in North America, such as Adderall XR and lisdexamfetamine have lower misuse liability. A recent study based on an American national survey for adults shows that rates of lifetime nonmedical use of prescription psychostimulants were relatively low (<2 per 100 000 prescriptions), and even lower for extended-release formulations (<1 per 100 000 prescriptions). Although Cochrane systematic reviews evaluating prescription psychostimulants, including PAs, for MUD and CUD showed no significant difference between psychostimulants and placebo regarding serious, cardiac and overall adverse effects, there continues to be controversy surrounding the appropriateness of prescribing PAs for patients with OUD, including those with PSUD.

The contamination of street supplies of stimulants with synthetic opioids adds even more potential risk to patients with OUD with co-occurring PSUD. Studies to date have not evaluated the risks of PAs in populations with co-occurring PSUD. This is particularly relevant nowadays when polysubstance use and co-occurring SUDs are highly prevalent in people with OUD. Furthermore, little is known on the risks of drug-related poisoning in patients with OUD with PSUDs who are receiving PAs. Given these gaps in research, the goals of this study were to: (1) investigate the impact of PAs on retention in OUD buprenorphine treatment; (2) provide the odds of SUD-related emergency admission or drug-related poisoning events in patients with OUD taking PAs; (3) compute the odds of SUD-related emergency admission or drug-related poisoning events among those with a concurrent OUD and a PSUD; this differs from previous work on the field as we focus solely on PAs (rather than prescription psychostimulants in general) and stratify our analyses between individuals with and without a PSUD.

**METHODS**

**Study design and data source**

This was a retrospective cohort study using the Merative MarketScan Commercial and Multi-State Medicaid Databases, which include comprehensive longitudinal clinical, enrolment and pharmacy data for clinical encounters and filled prescriptions across 50 states in the USA, as previously described. The study was conducted in two stages. We first analysed the relationship between PA prescriptions and retention in buprenorphine treatment in patients with OUD with and without co-occurring PSUD. Subsequently, among a subgroup of buprenorphine recipients who had any SUD-related emergency admissions or drug-related poisoning, we evaluated the within-person relationship between PA as a time-varying exposure and SUD-related events. Our data were available from 1 January 2006 to 31 December 2016. Analyses were conducted from 2 July 2022 to 5 March 2023.

**Participants and observation window**

The sample was derived from 250 958 insured people in the USA who had a diagnosis of OUD based on International Classification of Diseases (ICD)-9/ICD-10 codes and a 6-month minimum of pharmacy and medical coverage prior to the start of treatment, as this represents a standard baseline lookback period for covariate assessment. As shown in figure 1, we used a retrospective cohort design in two stages. In the first stage, we derived a cohort of 90 269 people with a diagnosis of OUD who received buprenorphine, for which we analysed patterns of treatment retention. Because we ascertained the relationship between PA exposure during the first 30 days of treatment and downstream buprenorphine discontinuation rates, we excluded 19 138 people who did not have at least 30 days of retention in buprenorphine. In the second stage, we evaluated the association between PA use and (1) SUD-related emergency admissions and (2) drug-related poisonings among people receiving buprenorphine treatment for OUD with each person serving as their own control in a repeatable event, retrospective case crossover design. Because this design requires that all people in the sample exhibit variation on the outcome, that is, must have at least one event, we excluded all people who did not experience at least one SUD-related emergency admission (n=63 947) or drug-related poisoning event (n=82 099). We created a window of observation of up to 365 days before and after each person’s first event (index event) and analysed data at the person-day level (ie, days nested within persons). In other words, the final dataset for the second stage of analysis contained one record per day per person. People were permitted to contribute multiple events as long as they occurred during a period of up to 1 year after the index event. Case periods were days when events occurred, whereas control periods were days when such events did not occur. The final samples comprised 26 322 people with OUD who had at least one emergency admission for SUD-related events and 8170 people with OUD who had at least one drug-related poisoning during insurance enrolment.

**Variables**

The primary predictor variable was exposure to PAs, operationalised as: (1) receipt of PAs during the first 30 days of buprenorphine treatment for the first stage of our study (retention) and (2) days on which PAs were used for the second stage of our analysis (SUD-related emergency admission and drug-related poisoning). We pulled PAs using generic names in the MarketScan drug files, encompassing amphetamine salts and lisdexamfetamine, as those medications have shown potential efficacy reducing drug use and promoting unsupervised stimulant abstinence.

PAs were characterised by drug strength, quantity dispensed, and days’ supply. We assumed that active prescriptions for PAs connoted medication consumption. Outcome variables included retention in buprenorphine treatment, that is, time

Open access

to treatment discontinuation (stage 1 of study) and the binary outcomes of any SUD-related emergency admissions or drug-related poisoning (stage 2 of study).

The primary outcome variable for the first stage of the study was 180-day retention in buprenorphine (binary variable: yes/no). As a secondary outcome variable, we computed retention in treatment as continuous (time-to-event) variable, operationalised as the number of days of the first treatment episode based on the date on which the last buprenorphine fill occurred. In detail, we defined buprenorphine treatment episodes by the continuous receipt, with no lapse in fills or dispensing, exceeding >45 days. There is heterogeneity in the thresholds for buprenorphine discontinuation used by previous studies.24 While some analyses have employed 30-day continuation thresholds,25 other analyses have used 60-day thresholds.26 As we are interested in treatment gaps as opposed to short-term discontinuation of buprenorphine, we employed 45 days as the threshold for discontinuity. However, sensitivity analyses were conducted using an array of different treatment thresholds (30 days, 60 days, 90 days).

The primary outcome variables for the second stage of the study were the binary variables of any SUD-related emergency admissions or drug-related poisoning. SUD-related emergency admissions were coded using ICD-9/ICD-10 codes encompassing any non-tobacco-related SUD, primary or otherwise (291.xx, 292.xx, 303.xx, 304.xx, 305.xx except for 305.1, F10, F16, F18-F19), including accidents, poisonings and overdoses.27 Drug-related poisoning was coded using ICD-9-ICD-10 codes recorded in medical claims based on the US Centers for Disease Control and Prevention’s codes for drug-related poisoning (online supplemental eTable 1 for full codes).27 We coded PSUD

Figure 1  Association of prescription amphetamine (PA) treatment (red) versus no PA treatment (blue) with days to buprenorphine discontinuation (x-axis). (A) Among people with and without psychostimulant use disorder (PSUD), n=90 269; (B) among people with PSUD, n=5980; (C) among people without PSUD, n=84 289.

Median: 139 days (no PAs) vs 158 days (PAs), χ²=85.5, p<.001

Median 97 days (no PAs) vs 114 days (PAs), χ²=11.1, p<.001

Median 143 days (no PAs) vs 164 days (PAs), χ²=89.1, p<.00
(primary predictor variable) using ICD-9/ICD-10 diagnostic codes obtained during a 6-month lookback period preceding and including the date of buprenorphine initiation.

Detailed information about other co-occurring psychiatric and SUDs were also obtained in the 6-month lookback period preceding and including the date of buprenorphine initiation. Covariates for our analyses in stage 1 included age at start of buprenorphine (in years), and ICD-9/ICD-10 diagnostic codes for: mood disorder (depression or bipolar disorder), anxiety disorders (comprise of post-traumatic stress disorder, generalised anxiety disorder, panic disorder, obsessive compulsive disorder, social anxiety, anxiety disorder unspecified) or co-occurring SUDs (alcohol, cannabis, sedative-hypnotics (benzodiazepines, Z-drugs), tobacco).

Statistical analyses
We computed descriptive statistics, evaluating the age, clinical characteristics (insurance status, race (among Medicaid enrollees), co-occurring SUDs, mood, anxiety and psychotic disorders) in the sample. Univariate analyses were computed using $\chi^2$ tests and the Wilcoxon rank-sum test. For stage 1 of our analysis, we used the Kaplan-Meier procedure to estimate the unadjusted time to buprenorphine discontinuation, stratifying by PSUD status. We used multivariable Cox proportional hazards regression models to estimate the time to buprenorphine discontinuation by PA use, with adjusted HRs obtained after controlling for covariates and accounting for multiple episodes per person. To further check the robustness of our results, we used a variety of different buprenorphine treatment gap definitions (30-day, 45-day, 60-day and 90-day) in sensitivity analyses.

Stage 2 of our analysis was conducted in a subgroup of people who had any SUD-related emergency admissions or drug-related poisoning. Our goal was to evaluate the association between PA treatment days and admissions and poisoning. The statistical details of the case-crossover procedure have been described previously. In brief, we compared—within the same individual—the association of event days with days of PA use (relative to days without medication use, which is the reference condition). Subsequently, we used conditional logistic regression to compute the odds of SUD-related events or drug-related poisoning as a function of medication, stratifying by a pre-existing diagnosis of PSUD in the 6 months before buprenorphine initiation. Secular time trends were controlled via the mathematical transformation to permit a flexible but non-linear association between time and outcome (restricted cubic spline). Sensitivity analyses were conducted that included the full spectrum of observation days beyond the 1 year before and after index event. All reported $p$ values were two-sided, with a significance level of 0.05. All analyses were conducted via SAS V9.4.

RESULTS
Prescription amphetamines and retention in buprenorphine
In the first stage of our analysis, the analytic sample contained 90,269 people spanning 119,892 treatment episodes initiating buprenorphine. Overall, 14,733 received PAs, whereas 75,534 did not; 39,891 (44.2%) were female (47.1% of those receiving PAs ($n=69,358$), 43.6% ($n=32,956$) of those not receiving PAs, $p<0.001$).

The mean age was 34.2 years (SD=10.3) for the PA group; 34.7 (11.5) for the non-PA group, $p<0.001$, and 21,256 persons (23.6%) had Medicaid insurance (2848 (19.3%): PA group; 18,408 (24.4%) non-PA group, $p<0.001$). Among Medicaid enrollees, 16,227 persons (81.0%) were non-Hispanic white (2458 (89.0%) for the PA group; 13,769 (79.7%) for the non-PA group, $p<0.001$). Co-occurring psychiatric disorders were common, with 22,677 (25.1%) having an anxiety disorder (4720 (32.0%) PA group; 17,957 (23.8%) non-PA group, $p<0.001$ and 18,714 (20.7%) having a mood disorder (4122 (28.0%) PA group; 14,592 (19.3%) non-PA group, $p<0.001$).

As depicted in table 1, 5980 persons (6.6%) had a diagnosis of PSUD in the 6 months before buprenorphine initiation (1223 (8.3%) among those who received PAs vs 4757 (6.3%) among those who did not receive PAs, $p<0.001$). More information about demographic characteristics of our sample can be seen in table 2.

In unadjusted analyses, Kaplan-Meier curves (figure 2) showed decreased likelihood of buprenorphine treatment discontinuation among individuals who received PAs (139 days non-PA group vs 158 days PA group, $\chi^2=85.5, df=1, p<0.001$), which remained significant in analyses limited to those with PSUD (97 days non-PA group vs 114 days PA group, $\chi^2=11.1, df=1, p<0.001$) and those without PSUD (143 days non-PA group vs 164 days PA group, $\chi^2=89.1, df=1, p<0.001$).

As shown in figure 3A, we observed consistent findings of improved 180-day buprenorphine retention associated with PAs. PA receipt was associated with increased buprenorphine retention for both those with co-occurring PSUD (adjusted risk ratio (aRR) 1.17 (95% CI 1.06 to 1.29)) and those without co-occurring PSUD (aRR 1.09 (95% CI 1.07 to 1.12)), which were sustained in subgroup analyses limited to Medicaid enrollees where we controlled for race/ethnicity (model B, online supplemental eTable 2). These effects remained robust at 360-day retention (model C, online supplemental eTable 2, people with PSUD, aRR 1.16 (95% CI 1.01 to 1.34); people without PSUD, aRR 1.14 (95% CI 1.11 to 1.18)), including in models controlling for race/ethnicity (model D, online supplemental eTable 2). As an additional sensitivity analysis, we computed Cox proportional hazards models for the risk of buprenorphine discontinuation, employing 30-day, 45-day, 60-day and 90-day gaps between buprenorphine episodes, which consistently illustrated protective effects of PA receipt on buprenorphine discontinuation risk (online supplemental eTables 3–5).

Prescription amphetamines and any SUD-related emergency admissions or drug-related poisoning
The second stage of our analysis evaluated 26,322 (spanning 25,470,786 person-days of observation time) people who had at least one SUD-related emergency admission and 8170 people (spanning 7,360,245 person-days of observation time), who had at least one drug-related poisoning event. As depicted in figure 3B, among people with and without a pre-existing diagnosis of PSUD, we observed similar magnitude of association between person-days of PA exposure and emergency admission for SUD-related event (OR 0.94 (95% CI 0.84 to 1.04) for OUD+PSUD; OR 0.82 (95% CI 0.76 to 0.88) for OUD without PSUD). As shown in figure 3C, among people with and without a pre-existing diagnosis of PSUD, we observed similar magnitude of association between person-days of PA exposure and admissions for drug-related poisoning (OR 0.96 (95% CI 0.75 to 1.23) for OUD+PSUD; OR 0.96 (95% CI 0.84 to 1.10) for OUD without PSUD).

DISCUSSION
Our findings show a considerable prevalence of co-occurring PSUD among individuals receiving treatment for OUD. Mood and anxiety disorders were also prevalent in our sample, as well

---

### Table 1 Clinical and demographic characteristics of the analytic sample

<table>
<thead>
<tr>
<th></th>
<th>All N=90269 persons (119892 episodes)</th>
<th>Received prescription amphetamines N=14735 persons (17441 episodes)</th>
<th>Did not receive prescription amphetamines N=75534 persons (102451 episodes)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-occurring psychostimulant use disorder</td>
<td>5980 (6.6)</td>
<td>1223 (8.3)</td>
<td>4757 (6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>34.2 (11.3)</td>
<td>31.9 (10.3)</td>
<td>34.7 (11.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medicaid (vs commercial insurance)</td>
<td>21256 (23.6)</td>
<td>2848 (19.3)</td>
<td>18408 (24.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race (among Medicaid only)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>16227 (81.0)</td>
<td>2458 (89.0)</td>
<td>13769 (79.7)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>958 (4.8)</td>
<td>58 (2.1)</td>
<td>900 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>222 (1.1)</td>
<td>36 (1.3)</td>
<td>186 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2630 (13.1)</td>
<td>210 (7.6)</td>
<td>2420 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>39891 (44.2)</td>
<td>6935 (47.1)</td>
<td>32956 (43.6)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50378 (55.8)</td>
<td>7800 (52.9)</td>
<td>42578 (56.4)</td>
<td></td>
</tr>
<tr>
<td>Co-occurring diagnoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>5221 (5.8)</td>
<td>3909 (26.5)</td>
<td>1312 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVD</td>
<td>13117 (14.5)</td>
<td>2161 (14.7)</td>
<td>10956 (14.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>22677 (25.1)</td>
<td>4720 (32.0)</td>
<td>17957 (23.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>18714 (20.7)</td>
<td>4122 (28.0)</td>
<td>14592 (19.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>1474 (1.6)</td>
<td>314 (2.1)</td>
<td>1160 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>7072 (7.8)</td>
<td>1420 (9.6)</td>
<td>5652 (7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sedative use disorder</td>
<td>3109 (3.4)</td>
<td>778 (5.3)</td>
<td>2331 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson Comorbidity Index computed based on co-occurring conditions during treatment</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>82711 (91.6)</td>
<td>13687 (92.9)</td>
<td>69024 (83.5)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5669 (6.3)</td>
<td>846 (5.7)</td>
<td>4823 (6.4)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>1889 (2.1)</td>
<td>202 (1.4)</td>
<td>1687 (2.2)</td>
<td></td>
</tr>
</tbody>
</table>

The Charlson Comorbidity Index quantifies a person’s non-psychiatric burden of disease, with higher scores indicating greater 1-year mortality risk. A cut-off of 2 or greater has been used as a threshold for greater burden of disease in people with substance use disorders.

ADHD, attention-deficit hyperactivity disorder; CVD, cardiovascular disease.

### Table 2 Clinical and demographic characteristics of the analytic sample

<table>
<thead>
<tr>
<th></th>
<th>All N=90269 persons (119892 episodes)</th>
<th>Received prescription amphetamines N=14735 persons (17441 episodes)</th>
<th>Did not receive prescription amphetamines N=75534 persons (102451 episodes)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-occurring psychostimulant use disorder in the 6 months preceding treatment initiation</td>
<td>5980 (6.6)</td>
<td>1223 (8.3)</td>
<td>4757 (6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>34.2 (11.3)</td>
<td>31.9 (10.3)</td>
<td>34.7 (11.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medicaid (vs commercial insurance)</td>
<td>21256 (23.6)</td>
<td>2848 (19.3)</td>
<td>18408 (24.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race (among Medicaid only)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>16227 (81.0)</td>
<td>2458 (89.0)</td>
<td>13769 (79.7)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>958 (4.8)</td>
<td>58 (2.1)</td>
<td>900 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>222 (1.1)</td>
<td>36 (1.3)</td>
<td>186 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2630 (13.1)</td>
<td>210 (7.6)</td>
<td>2420 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>39891 (44.2)</td>
<td>6935 (47.1)</td>
<td>32956 (43.6)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50378 (55.8)</td>
<td>7800 (52.9)</td>
<td>42578 (56.4)</td>
<td></td>
</tr>
<tr>
<td>Co-occurring diagnoses in the 6 months preceding treatment initiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>22677 (25.1)</td>
<td>4720 (32.0)</td>
<td>17957 (23.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>18714 (20.7)</td>
<td>4122 (28.0)</td>
<td>14592 (19.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>1474 (1.6)</td>
<td>314 (2.1)</td>
<td>1160 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>7072 (7.8)</td>
<td>1420 (9.6)</td>
<td>5652 (7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sedative use disorder</td>
<td>3109 (3.4)</td>
<td>778 (5.3)</td>
<td>2331 (3.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
as other SUDs such as alcohol and sedatives. Rates of PSUD diagnosis were higher in individuals receiving PAs. Importantly, we found that, in a sample of individuals with OUD, being prescribed a PA was associated with improved buprenorphine treatment retention rates among people with and without PSUD. Moreover, we found that being prescribed a PA does not confer an increase in the risk of SUD-related events or drug-related poisonings among people with OUD who are initiating buprenorphine; the presence of a co-occurring PSUD was not associated with increased drug-related poisoning risk relative to peers without PSUD.

The improved buprenorphine retention in patients receiving PAs, both with and without co-occurring PSUD, is a finding of potential clinical significance. This result is consistent with previous work by Mintz et al and extends the literature base by showing that people with co-occurring OUD and PSUD may also benefit from PA treatment. Improving retention in buprenorphine-based OUD treatment has been a challenge for clinical care and the present findings suggest that treatment of patients with co-occurring ADHD with prescription psychostimulants may improve their retention in OUD treatment.10 Furthermore, the treatment of ADHD in a SUD context is associated

Figure 2  Adjusted association of prescription amphetamine (PA) exposure with days until buprenorphine discontinuation. All models above adjusted for male sex, age, Medicaid status, co-occurring attention-deficit and hyperactivity disorder (ADHD) diagnosis, co-occurring cardiovascular disease, Charlson Comorbidity Index, co-occurring alcohol use disorder, co-occurring sedative use disorder, co-occurring anxiety disorder, co-occurring mood disorder, co-occurring psychotic disorder. Model 2A adjusted for co-occurring psychostimulant use disorders (PSUD vs no PSUD), whereas models 2B and 2C are stratified by presence of PSUD. Full models can be found in the online supplemental information. Model 2A corresponds to model 2A in online supplemental eTable 2 (45-day gap, highlighted in yellow). Model 2B corresponds to model 3A in online supplemental eTable 3 (45-day gap, highlighted in yellow). Model 2C corresponds to model 4A in online supplemental eTable 4 (45-day gap, highlighted in yellow).

Figure 3  Adjusted association of prescription amphetamine (PA) exposure with hospitalisation or emergency room admission for substance use disorders-related events (A), and hospitalisation or emergency admission for drug-related poisoning (B). PSUD, psychostimulant use disorder.
with improved ADHD symptoms,14 and it is well-established that patients with comorbid ADHD and SUDs should be treated for their ADHD with stimulant medications.28 Improving retention in treatment with buprenorphine has been shown to significantly decrease the risk of and related medical costs and therefore it confers those benefits in the population additionally treated with PAs.29

Our data also support the prescription of PAs for individuals with OUD receiving buprenorphine regardless of their PSUD status, as there appears to be no difference in risk for drug-related poisoning across PSUD status. A significant portion of individuals (21%) with OUD have ADHD30; existing literature shows that appropriate treatment is warranted as it improves ADHD outcomes.31 The findings of the present study show the initiation of PAs for ADHD in people initiating buprenorphine may be associated with improved OUD treatment retention, without marked increases in overdose risk. Importantly, we also observed decreased rates of emergency room admission for SUD-related events, consistent with previous research showing protective effect of ADHD medication against acute care utilisation for SUD-related events.13 27

The prior study by Mintz et al assessed any psychostimulant medication and found a modest increase in the risk of drug-related poisoning. We chose to focus solely on PAs in this study following recent evidence of their greater efficacy in treatment of PSUD as compared with other prescription psychostimulants.11 Similarly, a recent study has shown that the use of lisdexamfetamine is associated with a reduction in hospitalisations due to SUDs, any hospitalisations and all-cause mortality among individuals with MUD.32 suggesting there might be similar benefits to the agonist-based model for treatment for individuals with PSUD. It is plausible that this could reflect superior safety of PA formulations (i.e., lisdexamfetamine, amphetamine salts) relative to methylphenidate formulations included in the study by Mintz et al. The comparative SUD-related emergency admission and drug-related poisoning risks of different psychostimulant formulations (PA vs methylphenidate) warrant further investigation. This finding is also in contrast to the increased risk of poisoning found in individuals using ‘street’ stimulants contaminated with synthetic opioids, possibly because of the more favourable safety profile of buprenorphine as compared with synthetic opioids.2

Several key limitations should be considered. First, we cannot rule out residual confounding by unmeasured time invariant variables. Second, pharmacy claims for buprenorphine and stimulant fills do not always reflect consumption of medication. Third, our data predate the surge in synthetic opioid poisonings in the late 2010s and may not reflect risks posed by stimulant consumption together with fentanyl. Fourth, these results do not necessarily generalise to people without insurance or those who are not taking buprenorphine for OUD. While our findings suggest that buprenorphine initiators with PSUD are likely to benefit similarly from PAs as those without PSUDs, these data do not necessarily generalise to other populations of people with OUD and PSUD who are not connected to buprenorphine.

CONCLUSION
The prescription of PAs was associated with significant reduction in buprenorphine discontinuation risk in patients with OUD with and without co-occurring PSUD. We also found that having a co-occurring PSUD did not pose increased SUD-related emergency admission and drug-related poisoning risk associated with stimulant treatment among people with OUD taking buprenorphine. Future research is needed to evaluate the suitability and potential therapeutic benefits of PAs in the clinical care for individuals with OUD, especially for those with concurrent ADHD and PSUD.

Author affiliations
1Department of Psychiatry, Universidade Federal de Sao Paulo, Sao Paulo, Brazil
2Translational Addictions Research Lab, Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
3Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA
4Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York City, New York, USA
5Division of Substance Use Disorders, New York State Psychiatric Institute, New York City, New York, USA
6Department of Family and Community Medicine, Saint Louis University, St. Louis, Missouri, USA
7Department of Health and Outcomes Research, Saint Louis University, St. Louis, Missouri, USA

Twitter Vitor Tardelli @vitorstardelli

Acknowledgements The authors would like to thank Laura Bierut and Carrie Mintz for their thoughtful insights that contributed to this manuscript; Jeremy Goldbach and Kathleen Bucholz of the Transdisciplinary Training in Addictions Research (TransSTAR) T32 Programme of Washington University for obtaining funding to support effort for personnel (K.Y); in addition, the authors acknowledge Matt Keller, John Sahmann, Dustin Stwalley and the Centre for Administrative Data Research (CADR) at Washington University for assistance with data acquisition, management and storage. Merative and MarketScan are trademarks of Merative Corporation in the USA, other countries or both.

Contributors Concept: VT, K.YX, TMF, RAG, FRL. Design: VT, K.YX, TMF, RAG. Analysis of data: K.YX. Interpretation of data: VT, K.YX, TMF, RAG. Analysis of data: K.YX. Drafting of manuscript: VT, K.YX, TMF. Obtained funding: RAG. Administrative, technical or material support: RAG. Critical revision for important intellectual content: VT, K.YX, TMF, RAG, AB, FRL. Drafting of manuscript: VT, K.YX, TMF. Obtained funding: RAG. Administrative, technical or material support: RAG. Critical revision for important intellectual content: VT, K.YX, TMF, RAG, AB, FRL. K.YX is guarantor.

Funding This project was funded by R21 DA044744 (PI: RAG/Laura Bierut). Effort for some personnel was supported by grants T32 DA15035 (K.YX, PI: Kathleen Bucholz, Jeremy Goldbach), K12 DA041449 (K.YX, PI: Laura Bierut, Patricia Cavazos-Rehg), and by a fellowship from the Saint Louis University Research Institute (RAG) but these grants did not fund the analyses of the Merative MarketScan Multi-State Medicaid Database data performed by K.YX. CADR are funded in part by the Washington University Institute of Clinical and Translational Sciences via grants UL1 TR002345 (from the National Centre for Advancing Translational Sciences of the National Institutes of Health).

Competing interests AB received grants from National Institutes of Health (NIH), research support and medication samples from Alkermes, and consulting fees from OpheliaHealth, a telehealth provider for opioid use disorder. FRL reported consulting for Major League Baseball, receiving grants from the National Institutes of Health (NIH) and Substance Abuse and Mental Health Services Administration (SAMHSA), receiving a salary from the New York State Psychiatric Institute, and receiving non-financial support from US World Meds, Alkermes and Indivior outside the submitted work and serving as an uncompensated member of scientific advisory boards of Alkermes, Indivior, Novartis International, Teva Pharmaceutical Industries and US WorldMeds. RAG reported receiving grants from the NIH and Arnold Ventures during the conduct of the study, consulting for Janssen Pharmaceuticals and receiving personal fees for grant reviews from the NIH outside the submitted work.

Patient consent for publication Not applicable.

Ethics approval This study was exempt from institutional review board because no identifiable private data were used.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt and build upon this work non-commercially, provided the original work is properly cited. It is made available under the terms of the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits any non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Vitor Tardelli http://orcid.org/0000-0001-6040-7708

REFERENCES