HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Drug Alcohol Depend. 2017 January 01; 170: 9–16. doi:10.1016/j.drugalcdep.2016.10.039.

Psychoactive Medications and Disengagement from Office Based Opioid Treatment (OBOT) with Buprenorphine

Zoe M. Weinstein[a], **Debbie M. Cheng**[b], **Emily Quinn**[c], **David Hui**[d], **Hyunjoong Kim**[d], **Gabriela Gryczynski**[a], and **Jeffrey H. Samet**[a,e]

[a]Boston University School of Medicine/Boston Medical Center, Department of Medicine, Section of General Internal Medicine, Clinical Addiction Research and Education (CARE) Unit, 801 Massachusetts Avenue, 2nd Floor, Boston, MA 02118, United States

[b]Boston University School of Public Health, Department of Biostatistics, 801 Massachusetts Avenue, 3rd Floor, Boston, MA 02118, United States

[c]Boston University School of Public Health, Data Coordinating Center, 85 East Newton St, M921, Boston, MA 02118, United States

[d]Boston University School of Medicine, 72 East Concord St. Boston, MA 02118, United States

[e]Boston University School of Public Health, Department of Community Health Sciences, 801 Massachusetts Avenue, Boston, MA 02118, United States

Abstract

Background—The prevalence of psychoactive medications (PAMs) use in patients enrolled in Office Based Opioid Treatment (OBOT) and its association with engagement in this care is largely unknown.

Objective—To describe the use of PAMs, including those medications with emerging evidence of misuse (“emerging PAMs” - gabapentin, clonidine and promethazine) among patients on buprenorphine, and its association with disengagement from OBOT.

Corresponding Author: Zoe M. Weinstein, Section of General Internal Medicine, 801 Massachusetts Ave., 2nd floor, Boston, MA, 02118, 617-414-3707 (phone), 617-414-4676 (fax), zoe.weinstein@bmc.org.

Contributors: Zoe Weinstein, Colleen Labelle, Debbie Cheng and Jeffrey Samet participated in the design of the study. Zoe Weinstein managed the literature searches and summaries of previous related work. Zoe Weinstein managed the chart review process, sample selection, and database management with collaboration from David Hui, Hyunjoong Kim, Gabriela Gryczynski and Emily Quinn. Emily Quinn and Debbie Cheng undertook the statistical analysis, and Zoe Weinstein wrote the first draft of the manuscript. Zoe Weinstein, Jeffrey Samet, Emily Quinn and Debbie Cheng contributed to design of tables and figures. All authors contributed to and have approved the final manuscript.

Conflict of Interest: No conflict declared.

No funding sources had any role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Preliminary results were presented at the Addiction Health Services Research Conference, Marina Del Ray, California, October 2015 and the College on Problems of Drug Dependence Conference, Palm Springs, California, June 2016.

Methods—This is a retrospective cohort study of adults on buprenorphine from January, 2002 to February, 2014. The association between use of PAMs and 6-month disengagement from OBOT was examined using multivariable logistic regression models. A secondary analysis exploring time-to-disengagement was conducted using Cox regression models.

Results—At OBOT entry, 43% of patients (562/1308) were prescribed any PAM; including 17% (223/1308) on an emerging PAM. In separate adjusted analyses, neither the presence of any PAM (adjusted odds ratio [AOR] 1.07, 95% CI [0.78, 1.46]) nor an emerging PAM (AOR 1.28 [0.95, 1.74]) was significantly associated with 6-month disengagement. The results were similar for the Cox model (any PAM (adjusted hazard ratio [AHR] 1.16, 95% CI [1.00, 1.36]), emerging PAM (AHR 1.18 [0.98, 1.41])). Exploratory analyses suggested gabapentin (AHR 1.30 [1.05 – 1.62]) and clonidine (AHR 1.33 [1.01 – 1.73]) specifically, may be associated with an overall shorter time to disengagement.

Conclusions—Psychoactive medication use is common among patients in buprenorphine treatment. No significant association was found between the presence of any psychoactive medications, including medications with emerging evidence of misuse, and 6-month disengagement from buprenorphine treatment.

Keywords

buprenorphine; primary care; treatment retention; psychoactive medication

1. INTRODUCTION

Opioid use disorder (OUD) can be effectively treated with buprenorphine in an integrated primary care setting (Alford et al., 2011; Burns et al., 2015; Kraus et al., 2011; Padwa et al., 2012; Samet et al., 2001; Walley et al., 2012) and efforts to increase integrated addiction and primary care practices are currently underway (LaBelle et al., 2016; Ober et al., 2015; Rutkowski et al., 2012; Tai and Volkow, 2013; Volkow, 2014). This model of care is rapidly expanding, with 2.1 million ambulatory buprenorphine treatment visits in 2013, up from only 160,000 in 2003. This patient population has a high prevalence of psychiatric (Savant et al., 2013) and medical co-morbidities, including chronic pain (Wachholtz et al., 2011). Importantly, the success of OUD treatment can be compromised by poorly controlled psychiatric co-morbidities (Dausey and Desai, 2003; Kessler RC et al., 1994; Kraus et al., 2011; Savant et al., 2013).

Providers in integrated settings are faced with the difficult mission of optimizing patients' medical, psychiatric, and addictive disorders while simultaneously avoiding the iatrogenic harm of prescribing medications that may destabilize the patient. Unfortunately, it is not always clear which medications may be harmful versus beneficial. Benzodiazepines are associated with worse outcomes with buprenorphine: decreased retention in OUD treatment (Fareed et al., 2014; Ferri et al., 2014; Lee et al., 2014); increased risk of emergency room visits (Schuman-Olivier et al., 2013); accidental overdose; and death (Häkkinen et al., 2012; Reynaud et al., 1998; Sansone and Sansone, 2015; Seldén et al., 2012).

The majority of literature about the potential risk of psychoactive medications beyond benzodiazepines (e.g., gabapentin, clonidine and promethazine) is based on reviews of patients who either receive methadone for OUD or on opioids for chronic non-cancer pain (Baird et al., 2014; Lynch et al., 2015; Shapiro et al., 2013; Smith et al., 2015; Turner and Liang, 2015). Recently there are increasing numbers of case reports about the misuse potential of some commonly prescribed medications with psychoactive effects, specifically clonidine (Seale et al., 2014), gabapentin (Reeves and Ladner, 2014) and promethazine (Mendhekar et al., 1999; Zhou et al., 2008) in combination with buprenorphine. However, these psychoactive medications, especially gabapentin and clonidine, may be co-prescribed with buprenorphine to manage co-occurring psychiatric or sleep disorders and help maintain patients in recovery. While some psychoactive medications have been shown to increase the short-term (<12 weeks) tolerability of the opioid agonist induction or detoxification taper (Gold, 1993; Kleber et al., 1980; Kowalczyk et al., 2015; Salehi et al., 2011; Sanders et al., 2013; Washton and Resnick, 1982), their association with more long-term treatment outcomes have not been documented. Given the reports of misuse of gabapentin, clonidine and promethazine among patients on methadone and chronic opioids, as well as the emerging case reports for patients on buprenorphine, we hypothesized that these psychoactive medications would be associated with early disengagement from buprenorphine treatment. The goals of this study are to examine the proportion of patients receiving PAMs, and to assess whether these medications, including those with emerging evidence of misuse (“emerging PAMS” -gabapentin, clonidine and promethazine), are associated with early disengagement from an OBOT program.

2. MATERIALS AND METHODS

As part of the Disenrollment and Re-engagement in an OBOT Program (DROP) study, we performed a retrospective cohort analysis of adult patients treated with buprenorphine at the OBOT Program at Boston Medical Center January 1, 2002 to February 28, 2014 to describe the use of PAMs, and its association with the binary outcome of 6-month disengagement and the continuous outcome of time to disengagement.

2.1 Study setting

This OBOT program is housed within a primary care clinic at the largest safety-net medical center in New England. The program has been previously described, a collaborative care model, dubbed the Massachusetts Model (Alford et al., 2011; Substance Abuse and Mental Health Services Administration, 2014a). To be eligible to participate in the OBOT program, the patient must receive primary care at Boston Medical Center’s General Internal Medicine Primary Care Clinic, where OBOT is integrated. If the patient’s primary care physician (PCP) is properly credentialed to prescribe buprenorphine (i.e., waivered), then the same physician will typically serve this dual function of PCP and buprenorphine physician. If the patient’s PCP is not waivered, then one of the waivered physicians will conduct separate visits with the patient typically every 3 months or more often if indicated. The PCP and the buprenorphine physician will then co-manage the patient with the OBOT nurse care manager.

2.2 Study population

All adult patients who were established in care in the OBOT program during the study period were included in the analysis. For the purposes of this study, “established in care” was defined as having completed the intake process and undergone buprenorphine induction as evidenced by receipt of a prescription of buprenorphine with concurrent visits with a provider in the OBOT program. Although some patients disengaged and then subsequently re-engaged with the OBOT program, for the purposes of this study, we only used the first enrollment period for each patient.

2.3 Data sources and collection

All data were obtained from the Electronic Medical Record (EMR) at Boston Medical Center. Automated data reporting using the hospital’s Clinical Data Warehouse (Murphy, 2009) was used to compile basic registration and clinical data, including patient demographics, diagnoses, prescription history and laboratory results. When further clinical detail or clarification was required, two trained reviewers (D.H. and H.K.) manually reviewed clinic notes including standardized structured OBOT screening intake notes, OBOT nursing notes, and physician notes. In this manner we obtained details of patients’ substance use history and prior treatment for OUD. All documentation was originally created for clinical purposes by the OBOT program clinical team.

2.3.1 Outcomes—Our main outcome of interest was 6-month disengagement from OBOT. The secondary outcome was time to disengagement from OBOT. We considered patients to be “disengaged” from the OBOT program if they 1) had no active buprenorphine prescription for 60 days and 2) did not make any clinic contact for 60 days. The date of disengagement was designated the last day of an active prescription or clinic contact prior to meeting the disengagement criteria.

2.3.2 Main Independent Variables: PAMs and Emerging PAMs—The main independent variable was presence of any psychoactive medication (PAM) at the time of enrollment in OBOT. These medications were identified from the medication list from the EMR. Exploratory analyses also examined the presence of specific emerging PAMs (gabapentin, clonidine and promethazine), assessed both as a group (referred to as “any emerging PAM”) and as well as each emerging PAM separately. Additional analyses also explored the effect of the number of psychoactive medications (categorized as: 1, 2 or 3, or ≥ 4 medications) on disengagement outcomes.

2.3.3 Source of Medication Information—The EMR contained the original prescription date and refill dates for medications prescribed at the study site. The EMR also included medications prescribed by outside providers as documented as part of the medication reconciliation process at each medical visit. The dates medications were added and removed from the medication list were abstracted and used to assess for the presence of psychoactive medications (PAMs). The EMR did not record the indication or associated diagnoses for medications, and thus the indications for the medications are unknown. Additionally the EMR only represented the presence of a prescription, not whether the medication was filled or taken by the patient.

2.3.4 Psychoactive Medication Definition—We intentionally chose a broad definition of PAMs at the time of enrollment to include any medication used for mood symptoms or sleep. To create the PAM list, two physician authors (Z.M.W. and G.G.) each compiled an independent list of sleep and mood medications commercially available during the study period. These two lists were then combined, and reviewed by each party for omissions and redundancies. Before the list was finalized, it was again reviewed by the whole study group for omissions. In addition, we intentionally included additional medications that have psychoactive properties, even though that may not be their primary indication (i.e., gabapentin, clonidine, or promethazine). (Table 2 - full list of psychoactive medications)

2.3.5 Covariates—Potential confounders abstracted from the EMR and used in the multivariable analyses included age, race/ethnicity, gender, prior buprenorphine use, year of enrollment, and self-reported use of alcohol, cocaine and illicit benzodiazepines at time of enrollment. Marijuana use is not routinely collected in this clinic so it was not included.

Additional exploratory multivariable models examining PAM use were performed to assess the impact of psychiatric comorbidity as a potential confounder. Psychiatric comorbidities were collected from the problem list in the EMR. The limitations of a medical chart review as the source of the variable of “psychiatric diagnosis” are well established (Alaghehbandan et al., 2012; Fiest et al., 2014; Iezzoni, 1990; Noyes et al., 2011). First, psychiatric comorbidities are a heterogeneous group of diseases. Additionally, the source for determination of this variable was the presence of ICD-9 codes on the patient problem list. Those categorized as without a psychiatric diagnosis represent both patients free of disease, as well as those who are as yet undiagnosed. Given the limitations of this categorization we elected not to include psychiatric diagnosis in our main model, but instead to use in an additional set of exploratory analyses. Additionally, as patients were allowed to seek psychiatric care in other settings and these visits were not routinely visible in the EMR due to their confidential status, we were unable to reliably collect data on psychiatric visits.

2.4 Statistical Analyses

Descriptive statistics were calculated for baseline demographics and clinical characteristics. Frequencies and percentages were calculated for categorical patient factors. For continuous patient variables, means, medians, standard deviations and interquartile ranges were obtained.

To assess the association between PAMs and 6-month disengagement, unadjusted and adjusted logistic regression analyses were performed. The adjusted regression models controlled for potential confounders including age, race/ethnicity, gender, prior buprenorphine use, year of enrollment, and self-reported use of alcohol, cocaine and illicit benzodiazepines at time of enrollment. Odds ratios and 95% confidence intervals are reported for each model. Prior to regression analyses, Spearman correlation coefficients were calculated between independent variables and covariates, and no pair of variables had a correlation >0.40. Exploratory analyses assessing the number of PAMs, the presence of emerging PAMs, and the specific use of gabapentin, clonidine, and promethazine were conducted using the same approach described above.

Separate Cox regression models were used to assess the association between PAMs, the number of PAMs, presence of emerging PAMs, and the specific use of gabapentin, clonidine, and promethazine with the secondary outcome time to disengagement. Hazard ratios and 95% confidence intervals are reported for each model. Given the exploratory nature of the analyses, no adjustment was made for multiple comparisons. All analyses were completed using SAS 9.3 software (Cary, NC). The Boston University Medical Campus Institutional Review Board approved this study.

3. RESULTS

3.1 Sample characteristics

Over the 12-year study period, 1,308 patients were treated in the OBOT program. The majority were male (61.2%), white race (67.7%), unemployed (64.5%) and had completed high school or a more advanced degree (64.2%). Medical characteristics of these patients included high rate of smoking (82.0%) and psychiatric comorbidity (62.8%). The median buprenorphine dose was 16 mg per day and age at OBOT enrollment was 37 years. (Table 1)

3.1.1 Frequency of psychoactive medications on enrollment—On enrollment to OBOT, 43.0% (562/1,308) of patients had a prescription for any PAM. (Table 1) Additionally, 29.0% of patients had a prescription for more than one PAM on enrollment, with 18.9% (247/1,308) on two or three medications, and 10.1% (132/1,308) of patients prescribed four or more PAMs (data not shown). The most common medication class was selective serotonin re-uptake inhibitors (SSRIs), with 21.6% (283/1,308) prescribed this medication on enrollment. Medications for depression and anxiety were very common overall, with a fifth of patients (266/1,308) having prescription for “other antidepressants” (non-SSRIs including bupropion, trazodone and mirtazapine), 8.0% (104/1,308) a tricyclic antidepressant, 4.5% (59/1308) a non-benzodiazepine anxiolytic such as buspirone, and 3.4% (44/1,308) a serotonin–norepinephrine reuptake inhibitors (SNRIs). Antipsychotics and benzodiazepines were also regularly prescribed, with 13% (175/1,308) and 8.6% (113/1,308) of patients on these medications, respectively at enrollment (Table 2).

Medications defined as having emerging evidence for misuse were also frequently prescribed. On enrollment 17% (223/1,308) of patients were prescribed an emerging PAM (Table 1), including 11% (147/1,308) on gabapentin, 6.5% (85/1,308) on clonidine, and 2.6% (34/1,308) on promethazine. (Table 2)

3.2 Primary Outcome: 6-month Disengagement

3.2.1 Any PAM—Disengagement at 6 months was common, with 34.6% (453/1,308) of patients disengaging in the first 6 months of treatment. (Table 1) In adjusted logistic regression analyses, the presence of any psychoactive medication was not significantly associated with 6-month disengagement (Adjusted Odds Ratio [AOR] 1.07, 95 % CI [0.78, 1.46]). The covariates female gender and prior buprenorphine use (both illicit and prescribed) were associated with lower odds of 6-month disengagement. Patients who enrolled in the program during the latter years (i.e., 2008 – 2014) had higher odds of 6-month disengagement compared to those who enrolled during earlier years (i.e., 2002 to

2007). Black race/ethnicity, as compared to white race/ethnicity, was associated with increased odds of 6-month disengagement. (Table 3)

3.2.2 Emerging PAM—The presence of any emerging PAM on enrollment was also not significantly associated with 6-month disengagement from OBOT (AOR 1.04 [0.72, 1.50]). Similarly, no significant associations were detected in models for gabapentin (AOR 1.19 [0.78, 1.82]) clonidine (AOR 1.48 [0.87, 2.52]) or promethazine (0.56 [0.22, 1.40]). (Table 4)

3.2.3 Number of PAMs—Exploratory adjusted analyses did not detect an association between the number of medications on enrollment and the odds of 6-month disengagement. (Table 4)

3.3 Secondary Outcome: Time to Disengagement

3.3.1 Any PAM—The magnitude of effect of the main independent variable, presence of any PAM, in the multivariable Cox model (adjusted hazards ratio [AHR] 1.16, 95% CI [1.00 – 1.36]) was similar to that observed for the binary outcome, 6-month disengagement. The results did not reach statistical significance but were borderline. (Table 5) The covariates female gender and prior buprenorphine use (both illicit and prescribed) were associated with longer time to disengagement. Patients who enrolled in the program during the latter years (i.e., 2008 – 2014) had shorter time to disengagement compared to those who enrolled during earlier years (i.e., 2002 to 2007). A history of ever using heroin was also associated with shorter time to disengagement. (Data not shown)

3.3.2 Emerging PAM—In a separate multivariable Cox model, the group of emerging PAMs overall was not significantly associated with time to disengagement from OBOT (AHR 1.18 [0.98 – 1.41]), similar to the 6-month disengagement outcome. However in exploratory analyses assessing each emerging PAM separately, the presence of gabapentin (AHR 1.30 [1.05 – 1.62]) and clonidine (AHR 1.33 [1.01 – 1.73]) individually were significantly associated with shorter time to disengagement. (Table 5)

3.3.3 Number of PAMs—Compared to those with no psychoactive medications, having a prescription for only one PAM (AHR 1.06 [0.85 – 1.32]) did not appear to be associated with time to disengagement. Those with a prescription for multiple medications appeared to disengage in a shorter amount of time, however the results were significant only for those with two or three medications (AHR 1.24 [1.06 – 1.45]) but not those with four or more medications (AHR 1.15 [0.90 – 1.46]). (Table 5)

3.4 Additional Exploratory Analyses with Psychiatric Co-Morbidity

In the sample overall, 62.8% of patients had a psychiatric comorbidity, however 82.0% (461/562) of patients on any PAM, and 80.7% (180/223) of patients on emerging PAMs had a psychiatric diagnosis. To explore the impact of psychiatric comorbidity as a potential confounder, we ran the multivariable models again, including presence of a psychiatric diagnosis as an additional covariate. The findings of the repeated multivariable models were largely similar. For the outcome of 6-month disengagement, the adjusted odds ratios had

similar magnitude and direction and overall the results remained nonsignificant. In the Cox model of time to disengagement, the adjusted hazard ratio for any PAM (new AHR 1.38 [1.17 – 1.63]) reached significance with an increased magnitude of association. The adjusted hazard ratio for the emerging PAMs went from non-significant (AHR 1.18 [0.98 – 1.42]) to significant (new AHR 1.29 [1.07 – 1.55]). The results from gabapentin (new AHR 1.43 [1.15 – 1.78]) and clonidine (new AHR 1.41 [1.08 – 1.84]) remained significant with similar magnitudes of association as in the original model.

4. DISCUSSION

In this study we found a high prevalence of psychoactive medication (PAM) use, with 40% of patients having a prescription on enrollment to OBOT. Almost one-fifth of patients were prescribed more than one PAM, and a tenth were receiving four or more PAMs. These results are in the setting of a significant increase in polypharmacy among adults in the United States in recent years (Kantor et al., 2015), including a specific rise in psychotropic medications (Mojtabai and Olfson, 2010).

Currently, the medical community is being repeatedly reminded of the potential for iatrogenic harm from over-prescribing opioids and other psychoactive medications, which has contributed to the opioid epidemic (Jones and McAninch, 2015; Nelson et al., 2015; Substance Abuse and Mental Health Services Administration, 2014b; Turner and Liang, 2015). In a recent review of the rising national prevalence of psychoactive polypharmacy among outpatient psychiatrists, other researchers note that many of these medication combinations are not evidence-based and come with increased risk and unknown clinical benefit (Mojtabai and Olfson, 2010). In patients with OUD, potential additional risks of polypharmacy exist such as de-stabilization of OUD recovery (Caviness et al., 2013; Heikman et al., 2016; Wilens et al., 2015). However, these risks must be balanced with the need to manage patients' mood, sleep and pain symptoms to continue to keep them engaged in buprenorphine treatment.

We found a high prevalence of prescriptions for medications with emerging risk of misuse, including gabapentin, clonidine, and promethazine; in fact, gabapentin was the fourth-most prescribed psychoactive medication for patients in the study. Evidence of gabapentin misuse continues to be reported in general, and among patients with OUD, specifically (Smith et al., 2016). Some of the other commonly prescribed medications— including antipsychotics, especially quetiapine (Reeves and Ladner, 2014), as well as tricyclic antidepressants (Seale et al., 2014)—have been reported to be used non-medically by patients receiving buprenorphine to enhance the euphoric effects of the opioid. Many medications that were commonly prescribed in our study—including clonazepam, clonidine, and gabapentin—are known to be misused by patients with OUD seeking detoxification (Wilens et al., 2015). These medications are sedating and could contribute to hypoventilation, hypoxia and accidental overdose, especially in combination with an opioid (Kotlinska-Lemieszek et al., 2015).

Despite the many potential risks of PAMs, overall, there was not a significant association between PAMs (either in general or the emerging risk group) and either of the

disengagement outcomes. This finding may reflect that many of these medications are sedatives and anxiolytics and may increase the short-term tolerability of the buprenorphine induction and stabilization (Gold, 1993; Kleber et al., 1980; Kowalczyk et al., 2015; Salehi et al., 2011; Sanders et al., 2013; Washton and Resnick, 1982). However, in exploratory analyses assessing each emerging PAM separately, both gabapentin and clonidine appeared to be associated with shorter time to disengagement. Notably, the estimated effect sizes of all independent variables assessed were of similar magnitude and direction for both the dichotomous outcome of 6-month disengagement and the continuous outcome of time to disengagement. The Cox model is expected to have increased power to detect an effect, as the model accounts for the rate at which disengagement occurs over the entire course of the study rather than only at 6 months, which may explain the statistically significant findings for the two emerging PAMs. An important consideration when interpreting this study is confounding by indication. While a majority of patients on any PAM (82.0%) or an emerging PAM (80.7%) had a psychiatric diagnosis, this was not always the case. Patients diagnosed with more significant psychiatric, sleep and pain disorders may be more likely to be prescribed PAMs and may be more likely to disengage prematurely from treatment. Alternatively, some patients may be suffering with undiagnosed and untreated disease, while others are struggling with symptoms of early recovery (e.g., anxiety and insomnia) and thus being treated with PAMs but do not meet diagnostic criteria for an psychiatric disorder. Both of these latter two groups may be high risk to disengage from treatment. The former and latter two possibilities work in opposite directions with regard to the study's hypotheses. Thus, we ran additional multivariable models, including presence of a psychiatric diagnosis. We suspect our primary analyses may be a conservative estimate of the association between PAMs and disengagement as all hazard ratios either remained the same or increased with inclusion of psychiatric diagnoses. Given the limitations to the variable of "psychiatric diagnosis", including the source being on the ICD-9 codes on the patient problem list and lack of knowledge of active symptomatology and severity given the retrospective nature of this study, we elected not to include psychiatric diagnosis in our final model.

Notably, PAMs in general and emerging PAMs overall were not significantly associated with 6-month or time to disengagement, although exploratory analyses suggest two specific medications with emerging risk of misuse, gabapentin and clonidine, may be associated with shorter time to disengagement. As clonidine and gabapentin are not first line medications for any severe pain or psychiatric co-morbidity, it is unlikely those on these medications (as opposed to the other PAMs) represent the most severely ill patients. However, gabapentin and clonidine both represent medications commonly co-prescribed in detoxification settings and thus these medications may be a marker for patients whose opioid withdrawal symptoms are incompletely controlled on their current buprenorphine dose. Thus providers must continue to actively balance the benefit of these additional medications on patients' sleep, mood and pain symptoms with their risk of potential misuse.

The number of psychoactive medications did not significantly impact the odds of 6-month disengagement. However, those prescribed multiple (two or three) psychoactive medications appeared to be associated with shorter time to disengagement. This result is intriguing, speaking to the complex interplay of psychoactive medications and buprenorphine treatment outcomes. Those on none or only one psychoactive medication may have fewer co-

morbidities, and by comparison be relatively stable. While there was not a significant association for those on four or more medications, the hazard ratio had similar strength and directionality as compared to those on two or three medications, and may reflect the lower number of patients in this category and thus the analysis being underpowered to detect a significant difference.

The covariate results from the multivariable analyses are consistent with previous literature: prior buprenorphine use, whether illicit or prescribed, was associated with decreased risk of disengagement (Alford et al., 2011; Cunningham et al., 2013). Similarly, female gender was found to be negatively associated with disengagement in both models; prior literature shows that female patients have improved treatment retention (Burns et al., 2015; Öhlin et al., 2015). Consistent with some previous literature, black race was associated with increased odds of 6-month disengagement (Hser et al., 2014), however race was not significant in the Cox model. Later year of enrollment was associated with a higher risk of disengagement in both models. This may reflect the small and more highly selected patient population that participated in OBOT in the early years, relative to the more diverse and potentially less stable population that OBOT now serves as the program has expanded.

4.1 Limitations

This study has several limitations. As this was a retrospective chart review, with data originally collected for clinical purposes. As a single site retrospective study, generalizability is a concern; however, this collaborative care OBOT clinic is a model that has been disseminated for delivery of buprenorphine in primary care across the state of Massachusetts as well as sites across the United States (LaBelle et al., 2016; Substance Abuse and Mental Health Services Administration, 2014a). Additionally, we were not able to control for whether the patients were taking or misusing their medications, only the presence of an active prescription. As patients had different lengths of time in OBOT, we chose to explore the presence of PAMs on enrollment, not controlling for duration of therapy. While the association between PAMs and disengagement may be confounded by the indication for the medications, we attempted to address this by controlling for potential confounders in our multivariable model, examining the role of multiple medications, as well as specific classes of medications and performing additional analyses including psychiatric diagnoses as a covariate. Notably associations were only seen in medications that likely do not reflect the most severe medical or psychiatric co-morbidity.

4.2 Strengths

Despite these limitations, this study was able to capture the high prevalence of psychoactive medication use in a large cohort of patients prescribed buprenorphine over many years, a finding with limited previous assessment. The large number of patients, long follow-up time and wide range of medications offers a unique window into the complex interplay of psychoactive medications and buprenorphine treatment outcomes.

4.3 Conclusions

In this study, psychoactive medication use was common among patients in primary care Office Based Opioid Treatment (OBOT) with buprenorphine. Overall, these medications and

emerging-risk psychoactive medications (i.e., gabapentin, clonidine and promethazine) were not significantly associated with disengagement from OBOT care at 6 months. In exploratory analyses gabapentin and clonidine, specifically, appeared to be associated with shorter time to disengagement from buprenorphine treatment. Physicians and nurses who treat these patients need to be well versed in the management of psychoactive medications with increased awareness of the potential to impact retention in OBOT care.

Acknowledgments

The authors would like to thank Colleen Labelle RN for her assistance in study conception.

Role of Funding Source: The project described was supported in part by grant R25DA033211 from the National Institute on Drug Abuse, grant R25DA0123582 from the National Institute on Drug Abuse, grant T32AI52074 from the National Institute of Allergy and Infectious Diseases and grant 1UL1TR001430 from the National Center for Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse, National Institute of Allergy and Infectious Diseases or the National Center For Advancing Translational Sciences.

REFERENCES

Alaghehbandan R, MacDonald D, Barrett B, Collins K, Chen Y. Using administrative databases in the surveillance of depressive disorders—case definitions. Popul. Health Manag. 2012; 15:372–380. [PubMed: 22788998]

Alford DP, LaBelle CT, Kretsch N, Bergeron A, Winter M, Botticelli M, Samet JH. Collaborative care of opioid-addicted patients in primary care using buprenorphine: five-year experience. Arch. Intern. Med. 2011:171.

Baird CRW, Fox P, Colvin LA. Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers. Eur. Addict. Res. 2014; 20:115–118. [PubMed: 24192603]

Burns L, Gisev N, Larney S, Dobbins T, Gibson A, Kimber J, Larance B, Mattick RP, Butler T, Degenhardt L. A longitudinal comparison of retention in buprenorphine and methadone treatment for opioid dependence in New South Wales, Australia. Addiction. 2015; 110:646–655. [PubMed: 25516077]

Caviness CM, Anderson BJ, de Dios MA, Kurth M, Stein M. Prescription medication exchange patterns among methadone maintenance patients. Drug Alcohol Depend. 2013; 127:232–238. [PubMed: 22854293]

Cunningham CO, Roose RJ, Starrels JL, Giovanniello A, Sohler NL. Prior buprenorphine experience is associated with office-based buprenorphine treatment outcomes: J. Addict. Med. 2013; 7:287–293. [PubMed: 23722632]

Dausey DJ, Desai RA. Psychiatric comorbidity and the prevalence of HIV infection in a sample of patients in treatment for substance abuse. J. Nerv. Ment. Dis. 2003; 191:10–17. [PubMed: 12544594]

Fareed A, Eilender P, Ketchen B, Buchanan-Cummings AM, Scheinberg K, Crampton K, Nash A, Shongo-Hiango H, Drexler K. Factors affecting noncompliance with buprenorphine maintenance treatment. J. Addict. Med. 2014; 8:345–50. [PubMed: 25072677]

Ferri M, Finlayson AJR, Wang L, Martin PR. Predictive factors for relapse in patients on buprenorphine maintenance. Am. J. Addict. 2014; 23:62–67. [PubMed: 24313243]

Fiest KM, Jette N, Quan H, St. Germaine-Smith C, Metcalfe A, Patten SB, Beck CA. Systematic review and assessment of validated case definitions for depression in administrative data. BMC Psychiatry. 2014:14. [PubMed: 24443820]

Gold MS. Opiate addiction and the locus coeruleus. The clinical utility of clonidine, naltrexone, methadone, and buprenorphine. Psychiatr. Clin. North Am. 1993; 16:61–73. [PubMed: 8456048]

Häkkinen M, Launiainen T, Vuori E, Ojanperä I. Benzodiazepines and alcohol are associated with cases of fatal buprenorphine poisoning. Eur. J. Clin. Pharmacol. 2012; 68:301–309. [PubMed: 21927835]

Heikman P, Sundström M, Pelander A, Ojanperä I. New psychoactive substances as part of polydrug abuse within opioid maintenance treatment revealed by comprehensive high-resolution mass spectrometric urine drug screening. Hum. Psychopharmacol. Clin. Exp. 2016; 31:44–52.

Hser Y-I, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P, Wiest K, Cohen A, Ling W. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014; 109:79–87. [PubMed: 23961726]

Iezzoni LI. Using administrative diagnostic data to assess the quality of hospital care. Pitfalls and potential of ICD-9-CM. Int. J. Technol. Assess. Health Care. 1990; 6:272–281. [PubMed: 2203703]

Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am. J. Prev. Med. 2015; 49:493–501. [PubMed: 26143953]

Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States From 199–012. JAMA. 2015; 314:1818–1831. [PubMed: 26529160]

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of dsm-iii-r psychiatric disorders in the united states: results from the national comorbidity survey. Arch. Gen. Psychiatry. 1994; 51:8–19. [PubMed: 8279933]

Kleber HD, Gold MS, Riordan CE. The use of clonidine in detoxification from opiates. Bull. Narc. 1980; 32:1–10.

Kotlinska-Lemieszek A, Klepstad P, Haugen DF. Clinically significant drug-drug interactions involving opioid analgesics used for pain treatment in patients with cancer: a systematic review. Drug Des. Devel. Ther. 2015; 9:5255–5267.

Kowalczyk WJ, Phillips KA, Jobes ML, Kennedy AP, Ghitza UE, Agage DA, Schmittner JP, Epstein DH, Preston KL. Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: a randomized controlled trial with ecological momentary assessment. Am. J. Psychiatry. 2015; 172:760–767. [PubMed: 25783757]

Kraus ML, Alford DP, Kotz MM, Levounis P, Mandell TW, Meyer M, Salsitz EA, Wetterau N, Wyatt SA. Statement of the American Society of Addiction Medicine Consensus Panel on the use of buprenorphine in office-based treatment of opioid addiction. J. Addict. Med. 2011; 5:254–263. [PubMed: 22042215]

LaBelle CT, Han SC, Bergeron A, Samet JH. Office-Based Opioid Treatment with Buprenorphine (OBOT-B): statewide implementation of the Massachusetts Collaborative Care Model in community health centers. J. Subst. Abuse Treat. 2016; 60:6–13. [PubMed: 26233698]

Lee SC, Klein-Schwartz W, Doyon S, Welsh C. Comparison of toxicity associated with nonmedical use of benzodiazepines with buprenorphine or methadone. Drug Alcohol Depend. 2014; 138:118–123. [PubMed: 24629782]

Lynch KL, Shapiro BJ, Coffa D, Novak SP, Kral AH. Promethazine use among chronic pain patients. Drug Alcohol Depend. 2015; 150:92–97. [PubMed: 25754939]

Mendhekar DN, Sharma H, Dali JS. Case report of substance dependence with buprenorphine and mephentermine. Indian J. Psychiatry. 1999; 41:160–162. [PubMed: 21455380]

Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. Arch. Gen. Psychiatry. 2010; 67:26–36. [PubMed: 20048220]

Murphy, S. Data warehousing for clinical research. In: Liu, L.; Özsu, MT., editors. Encyclopedia of Database Systems. Boston, MA: Springer US; 2009. p. 679-684.

Nelson LS, Juurlink DN, Perrone J. Addressing the opioid epidemic. JAMA. 2015; 314:1453–1454. [PubMed: 26461995]

Noyes K, Liu H, Lyness JM, Friedman B. Medicare beneficiaries with depression: comparing diagnoses in claims data with the results of screening. Psychiatr. Serv. 2011; 62:1159–1166. [PubMed: 21969642]

Ober AJ, Watkins KE, Hunter SB, Lamp K, Lind M, Setodji CM. An organizational readiness intervention and randomized controlled trial to test strategies for implementing substance use disorder treatment into primary care: SUMMIT study protocol. Implement. Sci. IS. 2015:10. [PubMed: 25582164]

Öhlin L, Fridell M, Nyhlén A. Buprenorphine maintenance program with contracted work/education and low tolerance for non-prescribed drug use: a cohort study of outcome for women and men after seven years. BMC Psychiatry. 2015; 15:56. [PubMed: 25881164]

Padwa H, Urada D, Antonini VP, Ober A, Crevecoeur-MacPhail DA, Rawson RA. Integrating substance use disorder services with primary care: the experience in California. J. Psychoactive Drugs. 2012; 44

Reeves RR, Ladner ME. Potentiation of the effect of buprenorphine/naloxone with gabapentin or quetiapine. Am. J. Psychiatry. 2014; 171:691–691.

Reynaud M, Petit G, Potard D, Courty P. Six deaths linked to concomitant use of buprenorphine and benzodiazepines. Addict. Abingdon Engl. 1998; 93:1385–1392.

Rutkowski BA, Rawson RA, Freese TE. Editors' introduction: the evidence for integrated care-substance use disorders, mental health and primary care: California Substance Abuse Research Consortium (SARC) meetings, 2011. J. Psychoactive Drugs. 2012; 44:281–284. [PubMed: 23210375]

Salehi M, Kheirabadi GR, Maracy MR, Ranjkesh M. Importance of gabapentin dose in treatment of opioid withdrawal. J. Clin. Psychopharmacol. 2011; 31:593–596. [PubMed: 21869694]

Samet JH, Friedmann P, Saitz R. Benefits of linking primary medical care and substance abuse services: patient, provider, and societal perspectives. Arch. Intern. Med. 2001:161.

Sanders NC, Mancino MJ, Brooks W, Benjamin J, Bickel WK, Thostenson J, Oliveto AH. Randomized, placebo-controlled pilot trial of gabapentin during an outpatient, buprenorphine-assisted detoxification procedure. Exp. Clin. Psychopharmacol. 2013; 21:294–302. [PubMed: 23855333]

Sansone RA, Sansone LA. Buprenorphine treatment for narcotic addiction: not without risks. Innov. Clin. Neurosci. 2015; 12:32–36.

Savant JD, Barry DT, Cutter CJ, Joy MT, Dinh A, Schottenfeld RS, Fiellin DA. Prevalence of mood and substance use disorders among patients seeking primary care office-based buprenorphine/naloxone treatment. Drug Alcohol Depend. 2013; 127:243–247. [PubMed: 22771144]

Schuman-Olivier Z, Hoeppner BB, Weiss RD, Borodovsky J, Shaffer HJ, Albanese MJ. Benzodiazepine use during buprenorphine treatment for opioid dependence: clinical and safety outcomes. Drug Alcohol Depend. 2013; 132:580–586. [PubMed: 23688843]

Seale JP, Dittmer T, Sigman EJ, Clemons H, Johnson JA. Combined abuse of clonidine and amitriptyline in a patient on buprenorphine maintenance treatment. J. Addict. Med. 2014; 8:476–478. [PubMed: 25314340]

Seldén T, Ahlner J, Druid H, Kronstrand R. Toxicological and pathological findings in a series of buprenorphine related deaths. Possible risk factors for fatal outcome. Forensic Sci. Int. 2012; 220:284–290. [PubMed: 22565115]

Shapiro BJ, Lynch KL, Toochinda T, Lutnick A, Cheng HY, Kral AH. Promethazine misuse among methadone maintenance patients and community-based injection drug users. J. Addict. Med. 2013; 7:96–101. [PubMed: 23385449]

Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse, and diversion: a systematic review. Addiction. 2016 in press.

Smith RV, Lofwall MR, Havens JR. Abuse and diversion of gabapentin among nonmedical prescription opioid users in Appalachian Kentucky. Am. J. Psychiatry. 2015; 172:487–488.

Substance Abuse and Mental Health Services Administration. Medicaid coverage and financing of medications to treat alcohol and opioid use disorders. HHS publication no. SMA-14-4854. 2014a

Substance Abuse and Mental Health Services Administration. [accessed 11.16.15] Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. NSDUH Series H-48, HHS Publication No. (SMA) 14–4863. 2014b. [WWW Document]. URL http://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf

Tai B, Volkow ND. Treatment for substance use disorder: opportunities and challenges under the affordable care act. Soc. Work Public Health. 2013; 28:165–174. [PubMed: 23731411]

Turner BJ, Liang Y. Drug Overdose in a retrospective cohort with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: interactions with mental health disorders. J. Gen. Intern. Med. 2015; 30:1081–1096. [PubMed: 25650263]

Volkow, ND. [accessed 6.12.15] America's Addiction to Opioids: Heroin and Prescription Drug Abuse | National Institute on Drug Abuse (NIDA) [WWW Document]. 2014. URL http://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2014/americas-addiction-to-opioids-heroin-prescription-drug-abuse

Wachholtz A, Ziedonis D, Gonzalez G. Comorbid Pain and opioid addiction: psychosocial and pharmacological treatments. Subst. Use Misuse. 2011; 46:1536–1552. [PubMed: 21756033]

Walley AY, Tetrault JM, Friedmann PD. Integration of substance use treatment and medical care: a special issue of JSAT. J. Subst. Abuse Treat. 2012; 43:377–381. [PubMed: 23079197]

Washton AM, Resnick RB. Outpatient opiate detoxification with clonidine. J. Clin. Psychiatry. 1982; 43:39–41.

Wilens T, Zulauf C, Ryland D, Carrellas N, Catalina-Wellington I. Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. Am. J. Addict. 2015; 24:173–177. [PubMed: 25864607]

Zhou X, Zhang D, Wei H. A case of dependence on the combination use of sublingual buprenorphine, scopolamine, and promethazine. Addict. Disord. Their Treat. 2008; 7:109–112.

Highlights

- Psychoactive medication use is common among patients on buprenorphine treatment
- Psychoactive medications overall were not associated with 6-month disengagement
- Gabapentin, clonidine, and promethazine were not associated with 6-month disengagement

Table 1

Baseline Characteristics of OBOT Patients on Buprenorphine between 2002 and 2014 at Boston Medical Center Primary Care (N= 1308)

Demographics	**N (%) or median (IQR)**
Age (years) (N=1308)	37 (28, 46)
Male (N = 1292)	791 (61.2%)
Race/Ethnicity (N=1270)	
White	860 (67.7%)
Black	190 (15.0%)
Hispanic	202 (15.9%)
Other	18 (1.4%)
Employment status (N=1240)	
Unemployed	800 (64.5%)
Full or part time employment	255 (20.6%)
Disabled or retired	147 (11.8%)
Student	38 (3.1%)
Education (N=1045)	
Less than high school	374 (35.8%)
Completed high school or GED	318 (30.4%)
Some college or vocational Completed	128 (12.2%)
College	225 (21.5%)
Buprenorphine dose (mg) (N=1308)	16 (12, 16)
Smoking (N=868)	687 (82.0%)
Psychiatric Diagnosis	
Any diagnosis	821 (62.8%)
Depression	627 (47.9%)
Anxiety or Panic	394 (30.1%)
Bipolar or Mania	165 (12.6%)
Schizophrenia or psychosis	63 (5.0%)
ADHD	65 (5.0%)
Days to Disengagement /Censoring	316 (108,1021)
Disenrolled within the first 6 Months	453 (34.6%)
Prescribed a Psychoactive Medication	562 (43.0%)
Prescribed an Emerging Risk Psychoactive Medication	223 (17%)

Legend:
IQR – Interquartile range

Prescribed a Psychoactive Medication- On enrollment, prescribed at least one of the following: selective serotonin re-uptake inhibitor (SSRI), bupropion, trazodone, mirtazapine, tricyclic antidepressant, non-benzodiazepine anxiolytic, serotonin–norepinephrine reuptake inhibitor (SNRI), antipsychotic, benzodiazepine, gabapentin, clonidine or promethazine

Prescribed an Emerging Risk Psychoactive Medication – On enrollment, prescribed gabapentin, clonidine or promethazine

Table 2

Frequency of Individual Medication Classes on Enrollment among OBOT Patients (N= 1308)

Medications	**N (%)**
Any Psychoactive Medication	562 (43.0%)
SSRIs	283 (21.6%)
Other Antidepressants[a]	266 (20.3%)
Antipsychotics	175 (13.4%)
Gabapentin	147 (11.2%)
Benzodiazepines	113 (8.6%)
TCAs	104 (8.0%)
Clonidine	85 (6.5%)
Anxiolytics[b]	59 (4.5%)
Hypnotics[b]	53 (4.1%)
Mood stabilizers	47 (3.6%)
SNRIs	44 (3.4%)
Promethazine	34 (2.6%)

Legend:

SSRI- selective serotonin re-uptake inhibitors; TCA – tricyclic antidepressant; Other antidepressants[a]- bupropion, trazodone and mirtazapine; Anxiolytics[b] - non-benzodiazepine including hydroxyzine and buspirone; Hypnotics[b] - non-benzodiazepine including eszopiclone, zaleplon, zolpidem

Table 3

The Association Between Prescription of Any Psychoactive Drug and 6-month Disengagement from OBOT

Variable	Adjusted Odds Ratio (95% Confidence Interval)	p-value
Any Psychoactive Drug on Enrollment	1.07 (0.78, 1.46)	0.68
Female	0.71 (0.52, 0.98)	0.04
Current Alcohol Use	0.96 (0.64, 1.42)	0.82
Current Cocaine Use	1.42 (0.93, 2.16)	0.10
Current Benzodiazepine Use (Illicit)	1.28 (0.79, 2.07)	0.31
Current or History of Buprenorphine Use (Prescribed) **	0.29 (0.18, 0.47)	<.0001
Current or History of Buprenorphine Use (Illicit) **	0.48 (0.34, 0.69)	<.0001
History of Heroin Use	1.31 (0.79, 2.16)	0.29
Completed High school/GED	1.03 (0.75, 1.42)	0.84
Age of First Opioid Use	1.00 (0.98, 1.02)	0.96
Race/Ethnicity		
White	Reference	Reference
Black *	1.71 (1.10, 2.65)	0.02
Hispanic	1.14 (0.75, 1.74)	0.54
Other Race	0.42 (0.09, 1.94)	0.27
Year		
Enrolled 2003–2007	Reference	Reference
Enrolled in 2008–2010 **	2.64 (1.79, 3.89)	<.0001
Enrolled in 2011–2014 **	3.22 (2.02, 5.15)	<.0001

Legend:
History of heroin use – as compared to opioid pills only;

Completed High school/GED – graduated High school or passed the General Educational Development test

* $p < 0.05$;

** $p < 0.01$

Table 4

Associations between Medications with Emerging Risk of Misuse (Gabapentin, Clonidine and Promethazine), Multiple Psychoactive Medications and the Outcome 6-month Disengagement from OBOT

Model	Independent Variable	Adjusted Odds Ratio (95% Confidence Interval)	p-value
1^	Emerging Risk Group	1.04 (0.72, 1.50)	0.85
2^	Gabapentin	1.19 (0.78, 1.82)	0.43
3^	Clonidine	1.48 (0.87, 2.52)	0.15
4^	Promethazine	0.56 (0.22, 1.40)	0.22
5^	Number of Psychoactive Medications on Enrollment		
	0 medications	Reference	Reference
	1 medication	1.07 (0.69, 1.67)	0.76
	2–3 medications	0.97 (0.65, 1.44)	0.88
	≥4 medications	1.25 (0.78, 2.00)	0.36

Legend:
Emerging Risk Group – includes gabapentin, clonidine and promethazine;

^Reflects a separate multivariable model, each model includes controlling for the covariates: gender, race/ethnicity, education, age of first opioid use, current alcohol use, current cocaine use, current benzodiazepine use, history of heroin use, current or history of buprenorphine use (both prescribed and illicit), year of enrollment

*$p < 0.05$;

**$p < 0.01$

Table 5

Associations between Prescribed Any Psychoactive Medications, Multiple Psychoactive Medications, Medication with Emerging Risk of Misuse and the Outcome Time to Disengagement

Model^	Independent Variable	Adjusted Hazard Ratio (95% Confidence Interval)	p-value
1^	Any Psychoactive Medication	1.16 (1.00 – 1.36)	0.05
2^	Emerging Risk Group	1.18 (0.98 – 1.41)	0.08
3^	Gabapentin *	1.30 (1.05 – 1.62)	0.02
4^	Clonidine *	1.33 (1.01 – 1.73)	0.04
5^	Promethazine	0.76 (0.48 – 1.19)	0.22
6^	Number of Psychoactive Medications on Enrollment		
	0 Medications	Reference	Reference
	1 Medications	1.06 (0.85 – 1.32)	0.62
	2–3 Medications *	1.26 (1.04 – 1.53)	0.02
	≥4 Medications	1.15 (0.90 – 1.46)	0.26

Legend:
History of heroin use – as compared to opioid pills only; Emerging Risk Group –includes gabapentin, clonidine and promethazine;

^reflects a separate multivariable model, each model includes controlling for the covariates: gender, race/ethnicity, education, age of first opioid use, current alcohol use, current cocaine use, current benzodiazepine use, history of heroin use, current or history of buprenorphine use (both prescribed and illicit), year of enrollment

*p < 0.05;

**p < 0.01