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# Trajectory classes of opioid use among individuals in a randomized controlled trial comparing extended-release naltrexone and buprenorphine-naloxone★

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ABSTRACT

*Objectives:* To advance our understanding of medication treatments for opioid use disorders (OUDs), identification of distinct subgroups and factors associated with differential treatment response is critical. We examined trajectories of opioid use for patients with OUD who were randomized to (but not in all cases inducted onto) buprenorphine-naloxone (BUP-NX) or extended-release naltrexone (XR-NTX), and identified characteristics associated with each trajectory.

*Methods:* Growth mixture models (GMMs) were run to identify distinct trajectories of days of opioid use among a subsample of 535 individuals with OUD who participated in a 24-week randomized controlled trial (RCT; 2014–2016) of BUP-NX (n = 281) or XR-NTX (n = 254).

*Results:* Four distinct opioid use trajectory classes were identified for BUP-NX (near abstinent/no use (59%); low use (13.2%); low use, increasing over time (15%); and moderate use, increasing over time (12.8%)). Three distinct opioid use trajectory classes were found for XR-NTX (near abstinent/no use (59.1%); low use (14.6%); and moderate use, increasing over time (26.4%)). Across both BUP-NX and XR-NTX, the near abstinent/no use class had the highest number of medical management visits. Within BUP-NX, the low use class had a greater proportion of individuals with a previous successful treatment history compared with other classes. Within XR-NTX, the moderate use, increasing over time class had the highest proportion of Hispanic participants compared with other classes.

*Conclusions:* Findings highlight the significant heterogeneity of opioid use during a RCT of BUP-NX and XR-NTX and factors associated with opioid use patterns including medical management visits and history of treatment success.

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## 1. Introduction

More than 2.1 million people in the U.S. have an opioid use disorder (OUD), a chronic condition with 65%–84% of individuals relapsing within a month after completing inpatient or outpatient detoxification (Bailey et al., 2013; Day and Strang, 2011). Opioid overdose deaths have steadily increased over the last 15 years with 47,600 reported in 2017 (Center for Disease Control and Prevention, 2019). Synthetic opioids (other than methadone) such as the highly potent fentanyl, fentanyl analogs, and tramadol are responsible for more than half (29,000) of opioid-related overdose deaths (National Institute on Drug Abuse (NIDA), 2018); between 2002 and 2017 there was a 22-fold increase in the total number of overdose deaths attributable to synthetic opioids. Thus, there is a dire need to identify more effective and targeted methods of treating OUD.

Three pharmacologically distinct FDA-approved medications for OUD (MOUD) have been found to be effective, the full opioid agonist methadone, the partial agonist buprenorphine-naloxone [BUP-NX], and the antagonist naltrexone formulated as an extended-release injection [XR-NTX]. These are considered front-line treatments (Volkow, 2018) and traditionally combined with psychosocial interventions to provide comprehensive care. Methadone in the U.S. is only available in regulated specialty settings (i.e., Opioid Treatment Programs), while BUP-NX and XR-NTX can be prescribed across a range of healthcare settings, and have the potential to increase the accessibility of MOUD. BUP-NX and XR-NTX each have unique induction requirements portending distinct challenges in initiation and maintenance of treatment among patients. This is particularly true of XR-NTX which requires patients to be fully detoxified from opioids (e.g., no opioids for approximately 7–10 days; Jarvis et al., 2018); however, once induction hurdles are overcome, XR-NTX appear to be as effective as BUP-NX (Lee et al., 2018; Tanum et al., 2017). For example, a multi-site randomized controlled trial (RCT) comparing daily oral BUP-NX with flexible dosing (from 4 to 24 mg/day) to monthly intramuscular XR-NTX (380 mg) revealed no differences between the medications in reducing opioid and other illicit drug use in the short-term (i.e., 12 weeks; Tanum et al., 2017). A multi-site RCT in the United States, compared BUP-NX (administered sublingually via film) to XR-NTX (administered monthly via intramuscular injection), in a sample of individuals with OUD, over 24 weeks (Lee et al., 2018). Although significantly fewer participants successfully initiated XR-NTX, among those who were fully inducted on either XR-NTX or BUP-NX (per protocol treatment groups), there were no significant differences between the two treatments in weeks to relapse, opioid-negative urines, and self-reported opioid abstinent days. Thus, although XR-NTX may present unique induction challenges, studies support its efficacy as an additional treatment for OUD.

While the aforementioned trials provided important information on mean-level differences in rates of opioid use and relapse, there is scarce information on the variability in how individuals' opioid use changes over time while receiving MOUD. Identifying differential use patterns and treatment response and the characteristics that predict them is critical in understanding how MOUD work among subgroups of individuals, and can inform the timing and targeting of intervention efforts (Grella and Lovinger, 2011; Hser et al., 2017; Teesson et al., 2017). The limited research to date has demonstrated heterogeneity in opioid use trajectories for people on MOUD. In a sample of 795 people who use opioids and participated in a RCT of methadone or BUP-NX, Hser et al. (2017) identified 4 opioid use trajectories over time (up to 55 months posttreatment): low use, high use, decreasing use, and increasing use. More than 40% of the participants were in the low use group (demonstrating consistently low opioid use over time) after MOUD treatment. Eastwood and colleagues (2018) examined opioid use trajectories in a sample of 7719 individuals continuously enrolled in community based MOUD (methadone or buprenorphine) for at least five years and followed posttreatment for another two years. They found five heroin use trajectory classes: gradual decreasing, decreasing then increasing, continued low-level, rapid decreasing, and continued high-level (Eastwood et al., 2018). Variables that predicted non-response to treatment included current injection drug use, previous treatment, and higher social deprivation. These studies demonstrated variability in MOUD treatment response and highlight the benefit of adherence to treatment. Overall, studies show the strongest predictor of abstinence over follow-up was being on MOUD (Weiss et al., 2015). Findings underscore the need to identify treatment response early in the course of treatment to modify and optimize treatment interventions. Notably, no studies have examined patterns of treatment response during the first 24 weeks of treatment and in particular among patients randomized to XR-NTX.

The aim of this secondary analysis was to examine trajectories of opioid use for patients with OUD who were randomized to receive 24 weeks of treatment with either BUP-NX or XR-NTX, and to identify characteristics associated with each trajectory class. In particular, we were interested in exploring opioid use trajectories among individuals randomized to XR-NTX since this analysis had not previously been conducted.

## 2. Method

### 2.1. Study design and participants

This is a secondary data analysis of a multi-site 24-week open-label randomized effectiveness and safety trial comparing XR-NTX and BUP-NX for OUD. The detailed protocol (Lee et al., 2016; Nunes et al., 2016) and primary outcome analysis (Lee et al., 2018) have been previously published.

#### 2.1.1. Protocol

In brief, 570 individuals with OUDs were randomized to receive either XR-NTX or BUP-NX across eight community-based inpatient units affiliated with the National Drug Abuse Treatment Clinical Trials Network (intent-to-treat sample (ITT)). Participants were recruited following admission to inpatient treatment and were eligible if they had current OUD, no contraindications to initiation and treatment with either medication, and willing to accept randomization. Eligible participants were randomized to one of two treatment arms (BUP-NX of XR-NTX) in a 1:1 ratio, stratified by treatment site and opioid use severity. Study sites varied in detoxification protocols and durations, with some using tapers of methadone or buprenorphine and others using no opioids. Participants could be evaluated for the study, consented and randomized at any point flexibly after admission to the inpatient unit, so some were randomized "early" during tapers (i.e., within 72 h of last opioid use) and others "later" (i.e., more than 72 h following last opioid use). Per standard clinical guidelines, BUP-NX could be started once withdrawal symptoms began to emerge. For XR-NTX, patients needed to complete detoxification and wait until the urine toxicology converted to opioid negative and pass a naloxone challenge before medication could be initiated, presenting a significant induction hurdle. Participants were scheduled to receive XR-NTX injections (Vivitrol; Alkermes, Dublin, Ireland) every 28 days. In the BUP-NX arm, participants received sublingual film of Suboxone (Indivior, Slough, UK) for daily administration. BUP-NX was dispensed weekly for the first 4 weeks, and then at weeks 6, 8, 10, 12, 14, 16 and 20 at doses of 8–24 mg per day, adjusted per judgment of the treating physicians. Medical management visits (outpatient) involved building rapport and discussing psychosocial treatment recommendations, medication adherence, side effects, and opioid abstinence. Participants completed research assessments on a weekly basis during the 24 weeks of treatment. The per protocol sample consisted of 474 participants who were successfully inducted and received at least one dose of medication.

### 2.2. Measures

#### 2.2.1. Psychosocial measures

Demographic and OUD-relevant variables were assessed at baseline: gender, age, race/ethnicity and homelessness, age at opioid use onset, duration of opioid use, injection drug use status, history of successful past treatment, and whether this was participants' first opioid treatment episode. Opioid use was classified as severe if participants used six or more bags of heroin per day intravenously (Lee et al., 2018).

#### 2.2.2. Psychological measures

Participants were assessed via clinical interview for presence of anxiety or panic disorder, attention deficit hyperactivity disorder, bipolar and major depressive disorders. Participants' anxiety and depression severity, and the intensity of reported pain and discomfort, were assessed via the EuroQol-5 Dimension (EQ-5D; (Herdman et al., 2011; Janssen et al., 2013). Participant's history of psychiatric treatment was assessed by asking whether a participant had at least one treatment for any psychological or emotional problem in an inpatient or outpatient setting, not including substance abuse, employment, or family counseling.

#### 2.2.3. Treatment characteristic measures

Induction status (not inducted versus inducted), number of medical management weeks, and randomization timing (early versus late) were assessed.

#### 2.2.4. Outcome measure

The Time Line Follow Back method (TLFB; Sobell and Sobell, 1995) was used to assess self-reported days of opioid use over each two-week period (0–14 days) across the 24-weeks of treatment. A non-abstinent day was a positive response for use of any of the following: opioid analgesics, methadone, heroin, or buprenorphine (if not prescribed). Non-response to the self-report was treated as a missing value.

### 2.3. Statistical analyses

Growth mixture models (GMMs) were fit to identify distinct trajectory classes of days of opioid use over the 24-week treatment period for each treatment. A two-step classify-then-analyze approach was utilized (Kamata et al., 2018). In the first step (classify step), a series of GMMs were run using a zero-inflated Poisson distribution to match the distribution of the outcome. The models included from 2 to 6 classes, along with slope, intercept, and quadratic term. Each set of GMMs were run separately for each treatment group, and were run on the retained subsample (RS) of participants that had at least one TLFB value (n = 535). Analysis of baseline differences between those completely missing TLFB data versus the RS sample did not reveal any meaningful differences, and therefore, missingness due to completely unobserved TLFB values was not expected to lead to biased results.

The goodness-of-fit measures including Bayesian Information Criterion (BIC, lower is better), adjusted-BIC (lower is better), entropy (a measure of class separation ranging from 0 to 1, higher is better), and interpretability of the classes were used to assess optimal GMM class size for each treatment (Ram and Grimm, 2009). Additionally, Lo-Mendell-Rubin likelihood ratio tests (LMR-LRT) were used to test whether k classes significantly fit the data better than k-1 classes.

In the second step (analyze step), each participant was assigned to one class based on their most likely class membership (i.e., the class with the highest posterior probability) from the best fitting model. Then, bivariate analyses assessed whether induction success, patient characteristics, or time in medical management were associated with most-likely class membership within each treatment arm. Bivariate analyses were run using one-way ANOVAs for continuous measures and chi-square tests for categorical measures.

The GMMs were run using Mplus version 7, and all remaining analyses were run in SAS® 9.4. All hypothesis tests were two-sided with significance level of 5%.

**Table 1**
Patient characteristics of the overall ITT sample (n = 570) and the retained subsample (RS) with at least one observation included in the present analysis.

| | ITT sample (N = 570) | | RS with at least one outcome observation (N = 535) | |
|---|---|---|---|---|
| Measures | N | % or M (SD) | N | % or M (SD) |
| Induction Status | | | | |
| Not Inducted | 96 | 16.8 | 73 | 13.6 |
| Inducted | 474 | 83.2 | 462 | 86.4 |
| Gender | | | | |
| Male | 401 | 70.4 | 377 | 70.5 |
| Female | 169 | 29.6 | 158 | 29.5 |
| Age | 570 | 33.9 (9.6) | 535 | 33.8 (9.8) |
| Race | | | | |
| White Only | 421 | 73.9 | 396 | 74.0 |
| Black Only | 57 | 10.0 | 53 | 9.9 |
| Other | 92 | 16.1 | 86 | 16.1 |
| Hispanic Ethnicity (% yes) | 99 | 17.4 | 93 | 17.4 |
| Currently homeless (% yes) | 143 | 25.1 | 138 | 25.8 |
| Age at opioid use onset | 570 | 21.3 (7.1) | 535 | 21.3 (7.2) |
| Duration of Opioid Use (in years) | 570 | 12.5 (9.0) | 535 | 12.5 (9.1) |
| Intravenous Drug Use (% yes) | 385 | 67.5 | 365 | 68.2 |
| First Treatment Episode (% yes) | 209 | 36.7 | 197 | 36.8 |
| Any Past Tx Successful (% yes) | 224 | 39.3 | 208 | 38.9 |
| Anxiety/Depression | | | | |
| None | 179 | 31.4 | 165 | 30.8 |
| Moderate/Extreme | 391 | 68.6 | 370 | 69.2 |
| Pain/Discomfort | | | | |
| None | 235 | 41.2 | 216 | 40.4 |
| Moderate/Extreme | 335 | 58.8 | 319 | 59.6 |
| Any Psych Disorders (% yes) | 367 | 64.4 | 347 | 64.9 |
| History of Psych Tx (% yes) | 282 | 49.6 | 267 | 50.0 |
| Opioid Use Severity | | | | |
| Low | 343 | 60.2 | 322 | 60.2 |
| High | 227 | 39.8 | 213 | 39.8 |
| Randomization Timing | | | | |
| Early | 217 | 38.1 | 200 | 37.4 |
| Late | 353 | 61.9 | 335 | 62.6 |

## 3. Results

### 3.1. Descriptive statistics

Table 1 presents demographic characteristics for the intent-to-treat (ITT; N = 570) sample and the retained subsample (RS) of 535 participants who had at least one time point for the outcome observation. ITT participants were predominantly white men, with a mean age of 33.9 (SD = 9.6), single, unemployed, and Medicaid-insured. Approximately 17% self-identified as Hispanic. Sixty-eight percent used drugs intravenously, and overall had been using opioids, on average, for 12.5 years (SD = 9.0). Approximately 40% of the participants had high-severity opioid use (i.e. using 6 or more bags of heroin intravenously daily). The RS participants (n = 535) were more likely to have been inducted onto their treatment medication compared to those missing all outcome observations (n = 35, 86.4% vs 34.3%, respectively; $p < .001$). There were no other significant demographic or clinical characteristics differences between those with at least one outcome observation compared to those missing all outcome observations.

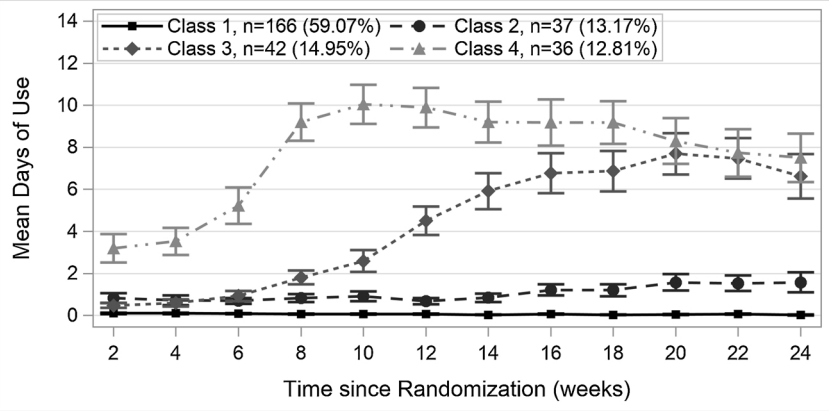


**Fig. 1.** Observed mean days of opioid use per 2-week interval with standard error bars by most likely trajectory class membership for BUP-NX participants.
Class 1: near-abstinent/ no use.
Class 2: low use.
Class 3: low use, increasing use over time.
Class 3: moderate use, increasing use over time.

### *3.2. Trajectories of days of opioid use for individuals randomized to receive BUP-NX*

The goodness-of-fit statistics for GMMs on participants randomized to BUP-NX with class sizes varying from 2 to 6 are presented in supplemental Table 1. There was a decreasing trend in both BIC and adjusted BIC, as well as a decreasing trend in entropy from models with classes 2 to 6. The Lo-Mendell-Rubin likelihood ratio test was significant from class sizes 2 to 4, but was not significant in the 5-class model. There was no significant improvement in model fit in the 5-class model compared to the 4-class model ($p = .114$), suggesting the 5-class model is not significantly better than the 4-class model. Additionally, in the 4-class model, the median posterior class probability was 1.00 (interquartile range = [0.994, 1.000]) with 88.3% of participants having a posterior class probability of 0.90 or more for their most likely class. Given these results and the clinically meaningful interpretability of the classes, the 4-class model was deemed the most parsimonious fit of the data.

Plots of observed mean days of self-reported opioid use per two-week period by most-likely trajectory class membership for BUP-NX participants are presented in Fig. 1. Participants in Class 1, the largest class (n = 166, 59.1%), had near abstinent use/almost no self-reported use (labeled as “near abstinent/no use”), on average, across the 24 week treatment period. Participants in Class 2 (n = 37, 13.2%) had, on average, low levels of use throughout the 24 week treatment period (labeled as “low use”). Participants in Class 3 (n = 42, 15.0%) had, on average, low levels of use immediately after entering treatment but their use steadily and moderately increased over the duration of the treatment period (labeled as “low use, increasing use over time”). Finally, participants in Class 4 (n = 36, 12.8%) had, on average, moderate use that increased and then stabilized during the treatment period (labeled as “moderate use, increasing use over time”).

Characteristics for the four trajectory classes based on most likely class membership for patients randomized to BUP-NX are presented in Table 2. Results revealed there were no statistically significant or clinically meaningful differences in demographic characteristics, age at opioid use onset, duration of opioid use, induction status, and psychological disorder or treatment measures among the four classes. There was a significant difference in history of past successful treatment among the classes ($p = .044$). Class 2 (low use) had the greatest proportion of participants with a history of successful treatment (54.1%) and Class 4 (moderate use, increasing use over time) had the lowest number of participants with a history of successful treatment (25.0%). There were significant differences in medical management weeks among the classes ($p < .001$). Class 1 (near abstinent/no use) had the highest number of medical management weeks (20.1 weeks) and Class 4 (moderate use, increasing over time) had the lowest number of medical management weeks (7.8 weeks).

### *3.3. Trajectories of days of opioid use for individuals randomized to receive XR-NTX*

The goodness-of-fit statistics for GMMs on XR-NTX participants with class sizes varying from 2 to 6 are presented in supplemental Table 2. There was a decreasing trend in both BIC and adjusted BIC, as well as a decreasing trend in entropy (except from 5 to 6 classes) from models with 2 to 6 classes. The Lo-Mendell-Rubin likelihood ratio test was significant from class sizes 2 to 3, but was not significant in the 4-class model, suggesting there was no significant improvement in model fit in the 4-class model compared to the 3-class model. ($p = .317$). Additionally, in the 3-class model, the median posterior class probability was 1.00 (interquartile range = [0.999, 1.000]) with 91.3% of participants having a posterior class probability of 0.90 or more for their most likely class. Given these findings and the interpretability of the classes, the 3-class trajectories model was deemed the most parsimonious fit of the XR-NTX participants’ data.

Plots of observed mean days of self-reported opioid use per two-week period by most-likely trajectory class membership for those randomized to XR-NTX are presented in Fig. 2. Participants in Class 1 (n = 150, 59.1%), the largest class, had near abstinent/almost no self-reported use, on average, across the 24-week treatment period (labeled as “near abstinent/no use”). Participants in class 2 (n = 37, 14.6%) reported, on average, low levels of use (approximately two to two and a half days of use every two weeks) until about weeks 18–24 when their use increased to about 3–5 days of use (labeled as “low use”). Participants in Class 3 (n = 67, 26.4%) reported, on average, moderate levels of use after starting treatment that increased over time, with slight decreases at weeks 22 and 24 (labeled as “moderate use, increasing use over time”).

Characteristics for the three trajectories based on most-likely class membership for patients randomized to XR-NTX are presented in Table 3. There were no statistically or clinically meaningful differences in age, gender, age of opioid use onset, years of opioid use, intravenous drug use, or psychological disorder measures among the three classes. There were statistically significant differences in the proportion of patients self-identified as Hispanic ($p = .017$), induction status ($p < .001$), history of psychiatric treatment ( = .024), and weeks of medical management ($p < .001$) among the three trajectory classes,

**Table 2**
Patient characteristics by most likely class membership, BUP-NX participants.

| | Class 1 Near-Abstinent/No Use (n = 166) | | Class 2 Low use (n = 37) | | Class 3 Low, Increasing Use (n = 42) | | Class 4 Moderate, Increasing Use (n = 36) | | Diff between classes (p-value)[a] |
|---|---|---|---|---|---|---|---|---|---|
| Measures | n | % or M (SD) | n | % or M (SD) | n | % or M (SD) | n | % or M (SD) | |
| Induction Status | | | | | | | | | 0.849 |
| Not Inducted | 8 | 4.8 | 2 | 5.4 | 1 | 2.4 | 1 | 2.8 | |
| Inducted | 158 | 95.2 | 35 | 94.6 | 41 | 97.6 | 35 | 97.2 | |
| Gender | | | | | | | | | 0.088 |
| Male | 113 | 68.1 | 30 | 81.1 | 35 | 83.3 | 23 | 63.9 | |
| Female | 53 | 31.9 | 7 | 18.9 | 7 | 16.7 | 13 | 36.1 | |
| Age | 166 | 34.2 (10.0) | 37 | 34.6 (10.4) | 42 | 33.5 (8.1) | 36 | 31.2 (10.5) | 0.400 |
| Race | | | | | | | | | 0.268 |
| White Only | 129 | 77.7 | 27 | 73.0 | 32 | 76.2 | 21 | 58.3 | |
| Black Only | 12 | 7.2 | 4 | 10.8 | 5 | 11.9 | 7 | 19.4 | |
| Other | 25 | 15.1 | 6 | 16.2 | 5 | 11.9 | 8 | 22.2 | |
| Hispanic Ethnicity (% yes) | 26 | 15.7 | 11 | 29.7 | 10 | 23.8 | 7 | 19.4 | 0.207 |
| Currently homeless (% yes) | 35 | 21.1 | 10 | 27.0 | 13 | 31.0 | 10 | 27.8 | 0.506 |
| Age at opioid use onset | 166 | 21.8 (8.2) | 37 | 20.6 (7.1) | 42 | 21.8 (7.3) | 36 | 20.7 (6.1) | 0.738 |
| Duration of Opioid Use (in years) | 166 | 12.3 (9.5) | 37 | 14.0 (9.2) | 42 | 11.7 (7.2) | 36 | 10.5 (9.3) | 0.424 |
| Intravenous Drug Use (% yes) | 114 | 68.7 | 27 | 73.0 | 30 | 71.4 | 21 | 58.3 | 0.527 |
| First Treatment Episode (% yes) | 66 | 39.8 | 7 | 18.9 | 19 | 45.2 | 16 | 44.4 | 0.059 |
| Any Past Tx Successful (% yes) | 54 | 32.5 | 20 | 54.1 | 16 | 38.1 | 9 | 25.0 | 0.044 |
| Anxiety/Depression | | | | | | | | | 0.570 |
| None | 53 | 31.9 | 8 | 21.6 | 11 | 26.2 | 12 | 33.3 | |
| Moderate/Extreme | 113 | 68.1 | 29 | 78.4 | 31 | 73.8 | 24 | 66.7 | |
| Pain/Discomfort | | | | | | | | | 0.390 |
| None | 70 | 42.2 | 10 | 27.0 | 16 | 38.1 | 15 | 41.7 | |
| Moderate/Extreme | 96 | 57.8 | 27 | 73.0 | 26 | 61.9 | 21 | 58.3 | |
| Any Psych Disorders (% yes) | 106 | 63.9 | 25 | 67.6 | 27 | 64.3 | 21 | 58.3 | 0.874 |
| History of Psych Tx (% yes) | 87 | 52.4 | 20 | 54.1 | 18 | 43.9 | 16 | 44.4 | 0.644 |
| Severity | | | | | | | | | 0.119 |
| Low | 108 | 65.1 | 17 | 45.9 | 22 | 52.4 | 21 | 58.3 | |
| High | 58 | 34.9 | 20 | 54.1 | 20 | 47.6 | 15 | 41.7 | |
| Randomization Timing | | | | | | | | | 0.108 |
| Early | 55 | 33.1 | 19 | 51.4 | 18 | 42.9 | 17 | 47.2 | |
| Late | 111 | 66.9 | 18 | 48.6 | 24 | 57.1 | 19 | 52.8 | |
| Weeks in Medical Management | 166 | 20.1 (6.7) | 37 | 18.3 (6.7) | 42 | 11.4 (3.8) | 36 | 7.8 (3.1) | < .001 |

[a] Differences between classes were assessed using one-way ANOVAs for continuous measures and chi-square tests for categorical measures.

while differences in housing status and randomization timing were notable but not significant (p-values just above 5% level of significance). Results revealed Class 3 (moderate use, increasing use over time; 23.9%) had the highest proportion of those who self-identified as Hispanic and Class 1 (near abstinent/no use; 10.0%) had the lowest proportion of those with Hispanic ethnicity. In terms of induction status: Class 1 (near abstinent/no use; 92.7%) had the highest proportion of participants who completed the naltrexone induction, followed by Class 2 (low use; 64.9%), and Class 3 (moderate use, increasing use over time; 44.8%). The association between Hispanic ethnicity and induction success was notable but not significant (p = .075). In terms of history of psychiatric treatment, Class 2 (low use; 70.3%) had the highest proportion of subjects who have received treatment for psychological or emotional problems, then Class 1 (near abstinent/no use; 46.7%) and Class 3 (moderate use, increasing use over time; 44.8%). In terms of medical management weeks: Class 1 (near abstinent/no use)

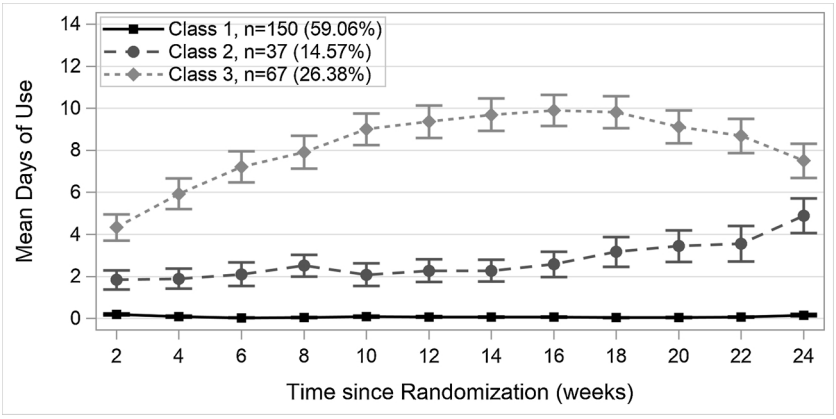


**Fig. 2.** Observed mean days of opioid use per 2-week interval with standard error bars by most likely trajectory class membership for XR-NTX participants.
Class 1: near-abstinent/ no use.
Class 2: low use.
Class 3: moderate use, increasing use over time.

**Table 3**
Patient characteristics by most likely class membership, XR-NTX participants.

| | Class 1 Near-Abstinent/No Use (n = 150) | | Class 2 Low Use (n = 37) | | Class 3 Moderate-Increasing Use (n = 67) | | Diff etween groups (p-value)[a] |
|---|---|---|---|---|---|---|---|
| Measures | n | % or M (SD) | n | % or M (SD) | n | % or M (SD) | |
| Induction Status | | | | | | | < .001 |
| Not Inducted | 11 | 7.3 | 13 | 35.1 | 37 | 55.2 | |
| Inducted | 139 | 92.7 | 24 | 64.9 | 30 | 44.8 | |
| Gender | | | | | | | 0.233 |
| Male | 100 | 66.7 | 30 | 81.1 | 46 | 68.7 | |
| Female | 50 | 33.3 | 7 | 18.9 | 21 | 31.3 | |
| Age | 150 | 33.4 (9.2) | 37 | 35.9 (10.4) | 67 | 33.7 (10.2) | 0.370 |
| Race | | | | | | | 0.256 |
| White Only | 114 | 76.0 | 28 | 75.7 | 45 | 67.2 | |
| Black Only | 17 | 11.3 | 2 | 5.4 | 6 | 9.0 | |
| Other | 19 | 12.7 | 7 | 18.9 | 16 | 23.9 | |
| Hispanic Ethnicity (% yes) | 15 | 10.0 | 8 | 21.6 | 16 | 23.9 | 0.017 |
| Currently homeless (% yes) | 46 | 30.7 | 13 | 35.1 | 11 | 16.4 | 0.051 |
| Age at onset | 150 | 21.0 (6.4) | 37 | 21.8 (7.3) | 67 | 21.1 (6.9) | 0.800 |
| Duration of Opioid Use | 150 | 12.5 (8.9) | 37 | 14.1 (9.6) | 67 | 12.6 (9.6) | 0.603 |
| IV Use (% yes) | 100 | 66.7 | 26 | 70.3 | 47 | 70.1 | 0.839 |
| First Treatment Episode (% yes) | 55 | 36.7 | 8 | 21.6 | 26 | 38.8 | 0.172 |
| Any Past Tx Successful (% yes) | 65 | 43.3 | 12 | 32.4 | 32 | 47.8 | 0.315 |
| Anxiety/Depression | | | | | | | 0.096 |
| None | 47 | 31.3 | 17 | 45.9 | 17 | 25.4 | |
| Moderate/Extreme | 103 | 68.7 | 20 | 54.1 | 50 | 74.6 | |
| Pain/Discomfort | | | | | | | 0.282 |
| None | 68 | 45.3 | 14 | 37.8 | 23 | 34.3 | |
| Moderate/Extreme | 82 | 54.7 | 23 | 62.2 | 44 | 65.7 | |
| Any Psych Disorders (% yes) | 95 | 63.3 | 30 | 81.1 | 43 | 64.2 | 0.115 |
| History of Psych Tx (% yes) | 70 | 46.7 | 26 | 70.3 | 30 | 44.8 | 0.024 |
| Severity | | | | | | | 0.522 |
| Low | 95 | 63.3 | 22 | 59.5 | 37 | 55.2 | |
| High | 55 | 36.7 | 15 | 40.5 | 30 | 44.8 | |
| Randomization Timing | | | | | | | 0.052 |
| Early | 46 | 30.7 | 13 | 35.1 | 32 | 47.8 | |
| Late | 104 | 69.3 | 24 | 64.9 | 35 | 52.2 | |
| Weeks in Medical Management | 149 | 19.9 (7.1) | 37 | 11.2 (6.8) | 67 | 8.3 (4.2) | < .001 |

[a] Differences between classes were assessed using one-way ANOVAs for continuous measures and chi-square tests for categorical measures.

had, on average, the highest number of medical management weeks (19.9 weeks), followed by Class 2 (low use; 11.2 weeks), and Class 3 (moderate use, increasing use over time; 8.3 weeks). Class 2 (low use) had the highest percentage of people who were homeless. Class 3 (moderate use, increasing use) had the highest proportion of patients who were randomized early.

## 4. Discussion

To advance our understanding of MOUD treatment response, the identification of distinct subgroups and factors associated with differential treatment response is critical to inform intervention efforts in terms of optimal targets and intervention leverage points. This secondary analysis identified four distinct opioid use trajectories for BUP-NX and three distinct opioid use trajectories for XR-NTX. Overall, the trajectory classes for XR-NTX and BUP-NX were quite similar (i.e., both had “near abstinent/no use”, “low use”, and “moderate use, increasing use over time” classes; BUP-NX had an additional class of “low use, increasing use over time”). We found the “near abstinent/no use” classes across both BUP-NX and XR-NTX treatments had the highest number of medical management weeks (mean of 20 weeks) relative to other classes. Medical management and adherence to treatment are deeply intertwined. Medical management focused on establishing and maintaining provider-patient rapport, reviewing medication adherence and side-effects and non-study opioid use, and promotion of use of psychosocial treatments. In contrast, those who were in the “moderate use, increasing use over time” class across both BUP-NX and XR-NTX attended only 7.8 and 8.1 weeks of medical management, respectively, suggesting interventions that increase attendance to medical management as well as adherence to MOUD, especially early in treatment, are needed. It is likely the medical management visits reflected general treatment adherence. Individuals who attended fewer medical management visits were less likely to receive or take their dose of BUP-NX or XR-NTX and thus, were more likely to relapse. Or conversely, those who relapsed were less likely to attend their medical management visits. Hser and colleagues (2017) also identified four opioid use trajectories for BUP-NX, however, their trajectories were different from those identified in this analysis. They found trajectories of low use, high use, decreasing use, and increasing use after treatment with methadone or buprenorphine-naloxone. Unlike Hser, we did not find a decreasing use trajectory for BUP-NX. Eastwood et al (2018) identified five trajectories of heroin use (gradually decreasing; decreasing then increasing; continued low-level; rapid decreasing; continued high level) over five years of treatment with methadone or buprenorphine. Eastwood et al.’s continued low-level subgroup is consistent with our low use subgroups; likewise, their decreasing then increasing subgroup is similar to BUP-NX’s low-use then increasing use class. Differences between the current and previous trajectory analyses are likely a function of differences in study and patient characteristics. The prior studies were multi-year posttreatment follow-up class analyses and this current analysis focused on identifying within treatment trajectory classes.

History of previous successful treatment emerged as an important pre-treatment variable distinguishing the BUP-NX classes, with a greater proportion of those in the low use group reporting prior treatment success. Given the chronic relapsing condition of OUD and the need for multiple treatment attempts, it makes sense that history of successful treatment is predictive of more positive treatment outcomes (Dennis et al., 2005). The finding that, among those randomized to XR-

NTX, more Hispanics were in the moderate use, increasing use over time trajectory class is also consistent with studies demonstrating poorer opioid use outcomes for those who are ethnic minorities (e.g., in Hser et al.'s (2017) sample, Hispanics were more likely to be in the high use group relative to the low use group). It is possible that the medical management services did not have the same benefit for Hispanics; or Hispanic identity may serve as a proxy for other variables such as social and environmental disadvantages that contribute to health disparities in general (Saloner and Cook, 2013; Windsor et al., 2015). Moreover, although all Hispanic patients enrolled in this trial were English-proficient, consideration of the ways in which language/cross-cultural barriers between patients and providers may be related to access and utilization of mental health and substance abuse treatment is imperative (Guerrero et al., 2013; Sentell et al., 2007). Finally, history of psychiatric treatment emerged as a significant pre-treatment variable distinguishing the XR-NTX classes, with a greater proportion of those in the low use group reporting receiving prior psychiatric treatment. It is unknown why this variable emerged as a significant distinguishing factor for the XR-NTX classes and not for those who received BUP-NX.

Several limitations must be noted. First, our opioid use outcome variable was based on self-reported drug use, which is subject to recall bias and social desirability effects. Nevertheless, self-reported substance use has been shown to correspond well with urine toxicology, when self-reports are elicited in research contexts where negative consequences will not ensue from acknowledging drug use (Clark et al., 2016; Wilcox et al., 2013). Second, our retained subsample included participants who were not successfully inducted onto an initial dose of study medication (4% of BUP-NX and 24% of XR-NTX participants), thus overall findings should be interpreted with caution. Some of the participants in the continuous opioid use classes were likely in those subgroups because they never started the medications. Given non-compliant participants tend to have poorer outcomes, their exclusion tends to overestimate the quality of the treatment outcomes. Thus, the advantage of using the retained subsample was that we avoided overestimating the benefits of MOUD (Gupta, 2011). Third, given BUP-NX and XR-NTX were initiated after participants completed inpatient detoxification and with varying induction strategies, findings may not be generalizable to those who initiate treatment in an outpatient setting. Fourth, several of our trajectory classes had small sample sizes, thus it is possible we were underpowered to detect significant differences among certain subgroups. In addition, although we examined an extensive array of demographic, psychosocial, and treatment characteristics, we likely did not measure all potential factors that could have differentiated the subpopulations.

Future research is recommended to replicate study findings with a larger, outpatient sample size and a greater number of predictors of trajectory class membership. Despite limitations, this study is one of the few clinical trials that have examined trajectories of opioid use during a RCT of BUP-NX and the first study to examine trajectories of use after randomization to XR-NTX.

The study findings have several implications for clinical treatment and policy. The largest subgroups across those randomized to receive BUP-NX or XR-NTX were in the no use/near abstinent groups, which was associated with attending more medical management appointments, underscoring the need for novel engagement strategies that increase medical management visits and treatment adherence. Contingency management and community reinforcement approaches have shown promise in these areas (Carroll and Weiss, 2016). The differential patterns of opioid use trajectories in MOUD treatment highlight the importance of providers regularly monitoring their patient's opioid use over time to anticipate treatment response and adjust treatment accordingly. Studies have shown that opioid use during the early weeks of treatment predicts poorer outcomes (Weiss and Rao, 2017). Thus, if a patient's opioid use is increasing over time, providers may consider either an increase in the current medication dosage, change in type of medication received, or an increase in psychosocial treatment or support that enhance treatment adherence (Murphy et al., 2007). More research is needed on the best medical or psychosocial strategy to improve prognosis among those with OUD. The findings that demographic factors such as ethnicity and homelessness were associated with particular opioid use trajectory classes emphasize the need for interventions tailored to these specific subpopulations. Enhancing recovery capital in the form of safe housing and additional social/treatment supports may help promote sustained abstinence from opioids (Groshkova et al., 2013; Laudet and White, 2008). In sum, our findings highlight the significant heterogeneity of opioid use during a RCT of MOUD treatment and several factors associated with longitudinal patterns of opioid use that can be effectively targeted in the context of active clinician monitoring and adaptive treatment strategies tailored to patient needs. Policies that increase access and adherence to MOUD treatment, alongside an understanding of the unique patterns of MOUD response and the factors that influence it, will be critical in reducing the current opioid crisis.

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## Contributors

LMR conceptualized and designed the research question. JS and MP conducted the statistical analyses. All authors drafted the initial manuscript, interpreted results, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

## Declaration of Competing Interest

The authors declare no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.107649.

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