Identifying Optimal Thresholds for Early Opioid Use Frequency in Predicting Buprenorphine Outcomes

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Abstract

Objective: Early prognostic indicators of nonresponse to buprenorphine treatment for opioid use disorder can inform targeted efforts to improve outcomes. Opioid use in the first 2–3 weeks of treatment predicts later outcomes, yet it is unclear what frequency of opioid use confers risk. We aimed to (1) identify thresholds for the frequency of early opioid use that optimally predict later sustained use and (2) quantify associations between thresholds and continuous treatment outcomes.

Method: We used data from 2 clinical trials of buprenorphine (N = 562; mean age = 34 years; 38% female), which were conducted from 2006-2009 and 2007-2011. Area under the receiver operating characteristic curve analyses identified optimal thresholds for opioid frequency during the first 4 weeks in predicting sustained use during weeks 5–12 (ie, 4 consecutive weeks with an opioid-positive or missing urine drug screen). Negative binomial regressions examined associations between early nonresponse and opioid-free and retention weeks.

Results: Sustained opioid use was optimally predicted by ≥1 day of opioid use in the first 2 weeks (sensitivity = 0.747; specificity = 0.688; positive predictive value [PPV] = 0.524; negative predictive value [NPV] = 0.856) and ≥2 days of use in the first 3 weeks (sensitivity = 0.649; specificity = 0.810; PPV = 0.611; NPV = 0.834). Both thresholds were negatively associated with opioid-free and retention weeks.

Conclusions: Even very low levels of opioid use in the first 2–3 weeks of buprenorphine treatment signal risk for poor outcomes. Emphasizing abstinence or near abstinence early in treatment might help promote long-term stability. Identified thresholds can be used to identify patients who may benefit from treatment adjustments and close monitoring.

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Buprenorphine is an effective treatment for opioid use disorder (OUD) that reduces illicit opioid use, overdose, and risk behaviors for infectious disease.[1] However, approximately 50% of patients receiving buprenorphine return to sustained opioid use or discontinue treatment prematurely.[2,3] Establishing early prognostic indicators of response to buprenorphine treatment can help to identify nonresponse quickly and inform personalized care through adaptive, stepped-care interventions.

In the Prescription Opioid Addiction Treatment Study (POATS), which evaluated buprenorphine treatment for prescription OUD, 71% of patients who were abstinent from opioids in both of the first 2 weeks of treatment reported abstinence or near abstinence in the last 4 weeks of treatment.[4] Conversely, 84% of those who used opioids in both of the first 2 weeks of treatment reported persistent use at the end of treatment.[4] A more recent analysis that harmonized data from 3 clinical trials, including POATS and trials of methadone and extended-release injectable naltrexone, found that opioid-positive urine drug screens in the first 3 weeks of treatment were the strongest predictor of return to sustained opioid use, outperforming a range of other variables (eg, baseline demographics, substance use severity, medical history, psychosocial factors).[5] Opioid use in the early phase of buprenorphine treatment clearly has predictive value; however, several gaps in knowledge remain.

Prior analyses have defined "early response" as continuous opioid abstinence and "early nonresponse" as opioid use in all of the first 2–3 weeks of treatment, primarily based on urine toxicology.[4,5] These definitions of early nonresponse can encompass a wide range of opioid use frequency patterns—from a single day of use in a week to daily use—and thus contribute to uncertainty regarding the *level* of use in the first few

Clinical Points

- Prior work has shown that opioid use in the first 2–3 weeks of buprenorphine treatment predicts poor outcomes, but it is unclear what level of opioid use confers risk.
- If a patient reports any illicit opioid use in the first 2 weeks of buprenorphine treatment or more than 1 day of use in the first 3 weeks, they may require close monitoring and adjustments to treatment to achieve success.
- Emphasizing abstinence or near abstinence in the first few weeks of buprenorphine treatment may help promote long-term stability.

weeks of treatment that confers risk. In other words, it is unknown whether both low-frequency (eg, 1–2 days) and high-frequency (eg, near-daily) opioid use early in treatment both indicate a risk for poor outcomes and need for additional support.

Defining early response to buprenorphine treatment based on a threshold of the number of days of opioid use that predicts later outcomes may offer greater precision in identifying individuals at risk for poor outcomes. We aimed to address this gap using a harmonized dataset of 2 clinical trials testing the addition of behavioral therapy to buprenorphine treatment,[6] including POATS,[2] as well as a trial enrolling participants who primarily used heroin rather than prescription opioids.[7] We first aimed to develop and internally validate a threshold for the number of opioid use days during the first 4 weeks of treatment that best predicted later sustained opioid use. In addition, prior studies of early response focused exclusively on binary opioid use outcomes, such as sustained opioid use[5] and end-of-treatment use.[4] To add nuance to assessments of early response, our second aim was to quantify associations between identified thresholds and continuous buprenorphine treatment outcomes, including the number of weeks participants were (1) retained in treatment and (2) opioid-free.

METHOD

Participants and Data Sources

We conducted secondary analyses of 2 randomized clinical trials (RCTs) of buprenorphine treatment (N = 562),[2,7] which are part of a larger National Institute on Drug Abuse–funded data harmonization study testing the addition of behavioral therapy to buprenorphine treatment.[6,8] This analysis was exempt from Mass General Brigham Institutional Review Board review.

Methods for both RCTs and the data harmonization study have been reported elsewhere.[2,6,7] Briefly, Study 1 participants (N = 653; enrolled in 2006–2009) were adults with *DSM-IV* prescription opioid dependence[9] enrolled in POATS.[2] In phase 1 of this 10-site outpatient study, participants received a 2-week buprenorphine-naloxone stabilization, a 2-week taper, and an 8-week follow-up. Those who returned to opioid use during phase 1 were eligible for phase 2, which included buprenorphine-naloxone treatment (8–32 mg/day) and standard medical management over 12 weeks, with or without additional behavioral counseling. Consistent with prior studies examining early response and the data harmonization study,[4–6] we included phase 2 data (N = 360).

Participants in Study 2 (N = 202; enrolled in 2007–2011) were adults who met criteria for *DSM-IV-TR*[10] opioid dependence (59% with primary heroin use). Participants received 2 weeks of buprenorphine-naloxone induction and stabilization, 16 weeks of buprenorphine-naloxone (8–24 mg/day) and randomized behavioral therapy conditions (ie, cognitive behavioral therapy, contingency management, and their combination), and 16 weeks of buprenorphine-naloxone alone, totaling 34 treatment weeks.[7]

Across studies, behavioral treatment conditions were combined, given no differences between conditions in primary opioid outcomes.[2,7] Participant demographics are reported in Table 1.

Measures

All measures were administered in both RCTs. Details on harmonization have been reported elsewhere.[6] Treatment length varied across these studies. Therefore, we examined the first 12 weeks (following the 2-week induction for Study 2) to facilitate harmonization.

Early treatment response. The Substance Use Report, a calendar-based method to collect daily substance use, was used for opioid use frequency within 4 periods during the first 4 treatment weeks: week 1, weeks 1–2, weeks 1–3, and weeks 1–4. Descriptive statistics for opioid use in each week are presented in Table 2.

Sustained opioid use. We defined *sustained opioid use* as 4 consecutive weeks with either an opioid-positive or missing urine drug screen result during weeks 5–12, similar to prior research examining early response to OUD medications.[5]

Opioid-free and buprenorphine retention weeks. As a continuous measure of opioid use, we examined the number of weeks that were opioid-free in weeks 5–12. An opioid use week was defined by *either* self-reported opioid use or opioid-positive urine drug screens.* We defined

*If participants self-reported no opioid use but had missing urine toxicology data for the same week (or vice versa, which was rarer), that week was coded as missing. Missing values were then imputed using a multiple imputation approach (see Supplementary Material) before calculating the total opioid-free weeks variable.

Table 1.
Participant Demographic Information[a]

	Total, N (%) or mean (SD)	Study 1, N (%) or mean (SD)	Study 2, N (%) or mean (SD)	Differences between studies, χ^2/t (*df*), *P* value
Sample size	562 (100%)	360 (64.0%)	202 (35.9%)	
Age	34.0 (11.0)	32.5 (9.7)	36.5 (12.6)	−3.87 (334.53), *P* < .001
Female sex	213 (37.9%)	151 (41.9%)	62 (30.7%)	6.49 (1), *P* = .011
Racial identity				42.56 (1), *P* < .001
White	462 (82.2%)	326 90.6%)	136 (67.3%)	
Black	28 (5.0%)	8 (2.2%)	20 (9.9%)	
Hawaiian/Pacific Islander	21 (3.7%)	0 (0.0%)	21 (10.4%)	
Multiracial	15 (2.7%)	6 (1.7%)	9 (4.5%)	
Asian	11 (2.0%)	2 (0.5%)	9 (4.5%)	
Native American	10 (1.8%)	7 (1.9%)	3 (1.5%)	
Other	12 (2.1%)	11 (3.1%)	1 (0.5%)	
Missing	3 (0.5%)	0 (0.0%)	3 (1.5%)	
Hispanic ethnicity	59 (10.5%)	18 (5.0%)	41 (20.4%)	30.88 (1), *P* < .001
Years of education	13.0 (2.1)	12.9 (2.2)	13.3 (2.0)	−2.01 (447.94), *P* = .045
Employment status				7.85 (1), *P* = .005
Full-time	296 (52.7%)	217 (60.3%)	79 (39.1%)	
Part-time	125 (22.2%)	67 (18.6%)	58 (28.7%)	
Unemployed	81 (14.4%)	50 (13.9%)	31 (15.3%)	
Student	35 (6.2%)	15 (4.2%)	20 (9.9%)	
Other	25 (4.4%)	11 (3.1%)	14 (6.9%)	
Marital status				13.49 (1), *P* < .001
Never married	313 (55.7%)	180 (50.0%)	133 (65.8%)	
Married	131 (23.3%)	102 (28.3%)	29 (14.4%)	
Divorced or separated	112 (19.9%)	75 (20.8%)	37 (18.3%)	
Widowed	5 (1.0%)	2 (0.4%)	3 (1.5%)	
Missing	1 (0.2%)	1 (0.3%)	0 (0.0%)	
Primary outcome: sustained opioid use in weeks 5-12	177 (31.5%)	96 (26.7%)	81 (40.1%)	10.21 (1), *P* = .001

[a]Information on gender identity was not collected. Chi-square tests examined differences between studies in those who were White vs non-White for racial identity, employed (full- or part-time) vs not employed for employment status, and married vs not married for marital status.

buprenorphine retention as the number of weeks that buprenorphine was dispensed and received, based on study records.

Data Analysis

All missing data were imputed using multiple imputation and the R package mice[11]; see Supplementary Materials for details.

Aim 1: Identifying thresholds for early response to buprenorphine treatment. Diagnostic test evaluation analyses were used to (1) identify optimal thresholds for opioid use frequency in each of the 4 periods (ie, week 1, weeks 1–2, weeks 1–3, and weeks 1–4) in predicting later sustained opioid use and (2) determine the earliest period at which thresholds demonstrated predictive utility. For each of the periods, we conducted area under the receiver operating characteristic curve (AUC-ROC) analyses with opioid use frequency classifying later sustained opioid use. AUC-ROC curves plot the sensitivity (true-positive rate) against 1 minus specificity (true-negative rate) for a range of thresholds, with optimal thresholds identified at the value where the sum of the sensitivity and specificity is maximized.[12–14†] We then calculated the positive predictive value (PPV) (true positive/[true positive+false positive]) and the negative predictive value (NPV) (true negative/[true negative+false negative]) for each threshold at each period. To assess internal validity and generalizability, we used bootstrapping (n = 100 resamples) to determine optimal threshold and applied these to out-of-bag data (ie, data held out for calculation of threshold). After conducting these analyses, we selected a definition of early response using the earliest threshold beyond which predictive performance no longer improved meaningfully. Analyses were conducted in R using the packages pROC[15] and cutpointr.[16]

Aim 2: Quantify associations between early response and opioid use and retention. We conducted negative binomial regression to examine associations between early

†We conducted sensitivity analyses that defined the threshold as the value where sensitivity and specificity were approximately equal, and results were unchanged.

Table 2.

Descriptive Statistics for Opioid Use and Frequency in Each Week in the First Month of Buprenorphine Treatment and Each Aggregated Period Used in Analyses

	Any opioid use, % (95% CI)	Days of use for participants with any use, Mean (SD)
Weeks in the first month		
Week 1	33% (29%–37%)	1.72 (1.30)
Week 2	31% (27%–35%)	1.76 (1.24)
Week 3	30% (26%–34%)	1.77 (1.33)
Week 4	28% (24%–32%)	1.90 (1.54)
Time periods used in analyses		
Weeks 1–2	45% (41%–49%)	2.46 (2.08)
Weeks 1–3	52% (48%–56%)	3.16 (2.73)
Weeks 1–4	57% (53%–61%)	3.81 (3.57)

response and opioid-free and buprenorphine retention weeks. An identity link function was specified to facilitate interpretation of model coefficients as the reduction in the expected number of weeks opioid-free or retained if a participant showed early nonresponse. To quantify the odds of sustained opioid use given early nonresponse, we also used logistic regression to examine associations between early response and sustained opioid use in weeks 5–12. All regression analyses controlled for study. Analyses were conducted using base R and the package MASS.[17]

RESULTS

Aim 1: Identifying Thresholds for Early Response to Buprenorphine Treatment

Table 3 presents the predictive power of opioid use frequency during each period in the first 4 weeks of treatment for later sustained opioid use, including the area under the curve (AUC), optimal thresholds, and associated sensitivity, specificity, PPV, and NPV. Opioid use frequency in all periods examined, except week 1, demonstrated acceptable discrimination (AUC > 0.70) between those who did and did not report sustained opioid use. Results from analyses of bootstrapped samples and out-of-bag data were nearly identical to those from the full sample (Table 4), suggesting that thresholds and associated performance metrics exhibited limited variability and generalized well to unseen data.

The optimal threshold for early nonresponse in weeks 1–2 was ≥1 day of opioid use (out of 14 days), and for weeks 1–3 and weeks 1–4, it was ≥2 days (out of 21 and 28 days, respectively). Although opioid use frequency in weeks 1–3 was only marginally better at predicting sustained opioid use compared to weeks 1–2, the two thresholds showed different strengths. The week 1–2 threshold demonstrated higher sensitivity (0.747) than specificity (0.688), suggesting that it may be more effective at capturing a broad group at risk for later sustained opioid use by reducing false negatives. In contrast, the week 1–3 threshold showed greater specificity (0.810) than sensitivity (0.649), indicating that it was better at minimizing false positives and more precisely capturing a smaller subset of individuals truly at risk for sustained use. Both thresholds had better NPV than PPV. Specifically, 86% (weeks 1–2) and 83% (weeks 1–3) of those below the thresholds (ie, early response) did not report later sustained opioid use (successful outcome), while 52% (weeks 1–2) and 61% (weeks 1–3) of those above the thresholds (ie, early nonresponse) did report sustained opioid use (unsuccessful outcome).

Opioid use frequency in weeks 1–4 provided only marginally better predictive performance than the earlier periods. Given our interest in identifying the earliest period in which opioid use frequency classified later outcomes, this period was not evaluated further.

Test of Aim 2: Quantify Associations Between Early Response and Opioid Use and Retention

Results from regression analyses examining associations between early response and opioid-related and retention outcomes are reported in Table 5. We also report descriptive statistics for each outcome by early response vs nonresponse and corresponding effect sizes.

Early nonresponse in weeks 1–2 was associated with 6.43 times greater odds of sustained opioid use in weeks 5–12, representing a large effect. In addition, early nonresponse during this period was associated with approximately 3.12 fewer opioid-free weeks (a large effect) and 1.11 fewer weeks retained in treatment (a small-to-medium effect).

Using the threshold identified for weeks 1–3, those with early nonresponse had 7.54 times greater odds of returning to sustained use, a large effect. Those with early nonresponse also reported approximately 3.70 fewer opioid-free weeks (a large effect) and 1.46 fewer weeks retained in treatment (a medium effect).

Exploratory Analyses

To better contextualize differences between the two identified thresholds, we specifically examined participants who used opioids on 1 day during weeks 1–3 (average sample size across imputations = 103) to (1) quantify the proportion whose 1 day of use was in weeks 1–2 (classified as early nonresponders according to the week 1–2 threshold, but early responders according to the week 1–3 threshold) vs those whose 1 day of use was in week 3 (classified as early responders

Table 3.

Predictive Power of Opioid Use Frequency in the First Month of Buprenorphine Treatment for Sustained Opioid Use in Weeks 5–12[a]

Time period	Optimal threshold	AUC	Sensitivity	Specificity	PPV	NPV	% Above threshold
Full sample							
Week 1	1	0.655	0.518	0.761	0.499	0.774	33
Weeks 1–2	1	0.752	0.747	0.688	0.524	0.856	45
Weeks 1–3	2	0.775	0.649	0.810	0.611	0.834	33
Weeks 1–4	2	0.788	0.722	0.771	0.592	0.858	38

[a]The optimal threshold was defined as the value where the sum of sensitivity and specificity was maximized. AUC = area under the curve; PPV = positive predictive value, defined as the proportion of participants above the optimal threshold who later demonstrated sustained opioid use; NPV = negative predictive value, defined as the proportion of participants below the optimal threshold who did not demonstrate evidence of later sustained opioid use.

Table 4.

Bootstrapping and Validation Performance of Predictive Models and Optimal Thresholds

	Bootstrapped performance (in-sample data)				Validation performance (out-of-bag data)		
Time period	Optimal threshold	AUC (95% CI)	Sensitivity	Specificity	AUC (95% CI)	Sensitivity	Specificity
Week 1	1.028	0.655 (0.610–0.699)	0.512	0.766	0.655 (0.597–0.713)	0.509	0.765
Weeks 1–2	1.077	0.752 (0.707–0.794)	0.733	0.702	0.752 (0.697–0.809)	0.726	0.700
Weeks 1–3	1.856	0.774 (0.732–0.817)	0.677	0.783	0.775 (0.719–0.831)	0.667	0.779
Weeks 1–4	1.988	0.788 (0.745–0.829)	0.725	0.769	0.787 (0.732–0.841)	0.722	0.767

Abbreviation: AUC = area under the curve.

Table 5.

Associations Between Early Response and Opioid-Related and Retention Outcomes[a]

Variable	Proportion (%) or mean (SD)		Cohen *h* or *d*	OR (95% CI) or b (SE)	*P* value
Weeks 1–2 definition	0 days of opioid use in weeks 1–2	≥1 day of opioid use in weeks 1–2			
Sustained opioid use in weeks 5–12	14.4%	52.4%	-0.84	6.43 (4.26–9.71)	<.001
Opioid-free weeks (weeks 5–12)	6.29 (2.37)	3.15 (2.94)	1.19	−3.12 (0.27)	<.001
Buprenorphine retention weeks (weeks 1–12)	11.10 (2.47)	9.93 (3.46)	0.39	−1.11 (0.29)	<.001
Weeks 1–3 definition	0–1 days of opioid use in weeks 1–3	≥2 days of opioid use in weeks 1–3			
Sustained opioid use in weeks 5–12	16.6%	61.1%	-0.96	7.54 (5.00–11.37)	<.001
Opioid-free weeks (weeks 5–12)	6.12 (2.40)	2.42 (2.74)	1.47	−3.70 (0.24)	<.001
Buprenorphine retention weeks (weeks 1–12)	11.1 (2.42)	9.55 (3.72)	0.53	−1.46 (0.31)	<.001

[a]We report Cohen *h* and odds ratios (ORs) and 95% confidence intervals for the binary sustained opioid use outcome. We report Cohen *d* and unstandardized betas (b) and standard errors (SEs) for the opioid-free weeks and buprenorphine retention weeks outcomes. All regression analyses controlled for study.

according to both thresholds), and (2) examine whether outcomes differed between these two groups. Of those with 1 day of use during weeks 1–3, most (73.2%) used during the first 2 weeks. There were no significant differences in treatment outcomes based on the timing of the 1 day of use: sustained opioid use (odds ratio [OR] = 0.80, 95% CI = 0.26–2.42), opioid-free weeks (b [SE] = 0.09 [0.69], $P = .896$), and retention weeks (b [SE] = −1.04 [0.85], $P = .220$). Notably, most participants who used 1 day in weeks 1–2 did not report use in week 3 (71.1%), while a minority reported use in week 3 and were also classified as nonresponders using the week 1–3 threshold (28.9%).

DISCUSSION

Using data from 2 clinical trials of buprenorphine for OUD, we identified thresholds for opioid use frequency during the first 2 and 3 weeks of treatment that displayed predictive value for later sustained use. Specifically, 52% of individuals reporting *any opioid use* in the first 2 weeks went on to sustained use, compared to 14% who were abstinent during this period. Similarly, 61% of individuals with *2 or more days of use* in the first 3 weeks reported sustained use, compared to 17% with 1 or no days. Those who showed early nonresponse using these thresholds reported approximately 3–4 fewer

opioid-free weeks during weeks 5–12 of treatment and 1–1.5 fewer weeks retained in buprenorphine treatment compared to those with good early response. Notably, self-reported opioid use frequency might have advantages over urine toxicology for assessing early response, including reduced burden on patients and providers, easy integration into remote appointments, and increasing trust in patient-provider relationships.[18]

We found that even very low levels of opioid use in the first 3 weeks of buprenorphine treatment signaled risk for poor outcomes. Yet, if opioid use can remain isolated to a single day within the first 3 weeks, potentially by framing this episode as a learning opportunity,[19] risk may be mitigated. This clinical implication is underscored by exploratory findings that those with 1 day of opioid use in weeks 1–2 but no use in week 3 were at relatively low risk of poor outcomes. Conversely, 2 or more days of use in the first 3 weeks might represent the beginning of a sustained use pattern. As such, emphasizing abstinence or near abstinence in the early weeks of buprenorphine treatment may promote stability and longer-term success.

These easily interpretable thresholds may also help identify patients requiring additional support to achieve success. Future research should investigate mechanisms contributing to early nonresponse and evaluate stepped-care interventions that may enhance outcomes. For example, illicit opioid use early in the treatment period that is driven by craving or withdrawal may indicate a need for a higher buprenorphine dose, while poor medication adherence may suggest benefit from extended-release formulations. Physicians in both studies could adjust buprenorphine doses throughout the trial when clinically indicated,[2,7] yet standardized guidelines to guide dose adjustments (ie, any use in the first 2 weeks) might optimize patient outcomes. Furthermore, early nonresponders may require higher doses than provided in these studies, particularly Study 2, which had a dose limit of 24 mg/day rather than 32 mg/day.[20] Alternatively, illicit opioid use driven by negative affect, social influences, or environmental cues may point to the need for adjunctive behavioral interventions (eg, cognitive behavioral therapy) or other psychosocial supports (eg, intensive case management). Those with poor early response might also benefit from discussions about strategies to reduce the harms of opioid use (eg, using opioids via non-intravenous routes, using with other people who have naloxone)[21] and targeted efforts to increase retention in treatment, including contingency management with rewards for attendance and transitioning to integrated care models.[22]

Notably, the early response thresholds demonstrated unique strengths, indicating suitability for different stepped-care strategies. The week 1–2 threshold (≥1 day of opioid use) showed relatively higher sensitivity and thus captured a broader group potentially at risk for poor outcomes. This conservative threshold may help guide close observation and low-cost, low-effort interventions (eg, increasing the buprenorphine dose), particularly for those who use only on 1 day and might not meet the week 1–3 definition of nonresponse. In contrast, the week 1–3 definition of early nonresponse (≥2 days of opioid use) showed relatively higher specificity, indicating that it may be a better fit for informing intensive or costly interventions, such as certain behavioral interventions (eg, contingency management). Both thresholds had better NPV (identifying those likely to have good outcomes) than PPV (identifying those at risk for poor outcomes). As such, future work might incorporate baseline predictors of poor outcomes (eg, intravenous drug use)[5,23] and other subjective reports in the first weeks of treatment (eg, craving, withdrawal) to optimize prediction of later sustained opioid use. In addition, examining baseline predictors of early nonresponse (using identified definitions) might help identify those requiring additional support even earlier in the treatment episode.

Results of the present study should be interpreted within the context of several limitations. First, data were collected before synthetic fentanyl dominated the drug supply,[24] and there may be different early nonresponse thresholds and prevalence rates in those who primarily use fentanyl. Our sample was largely non-Hispanic and white, underscoring the need to replicate findings in a more racially diverse sample. Although participants in Study 2 received buprenorphine treatment for 34 weeks, we used the first 12 weeks of treatment for outcome measures.[6] Research is needed to evaluate the predictive utility of early response over longer-term follow-up periods, given that real-world buprenorphine treatment often extends beyond 12 weeks.[25] Similarly, future research is needed to evaluate the generalizability of identified thresholds in naturalistic samples, particularly given some considerations with the clinical trials included in the present study. For example, participants in Study 1 (ie, POATS) were included in this analysis if they returned to opioid use following a buprenorphine taper and required a more intensive treatment phase.[2] In addition, 2 prior studies of early response have also used POATS data,[4,5] highlighting a need to examine this question in novel datasets, particularly those enrolling participants with fentanyl use. Our data sources also have strengths, including the frequent collection of data on opioid use, early in treatment, and with validated measures. Of note, we aggregated opioid use frequency at the weekly level to reflect clinical practice in which patients might meet with providers weekly to discuss progress and treatment modifications. With recent advances in real-time data collection and intervention delivery,[26] future research could examine more granular assessments of opioid use during the early treatment period (eg, time to

first reported use after initiation) and their associations with treatment outcomes.

Overall, patients receiving buprenorphine who report even very low levels of illicit opioid use in the first weeks of treatment—including any use in the first 2 weeks and more than 1 day of use in the first 3 weeks—may need close observation and treatment adjustments (eg, increased dose, switching formulations, adjunctive behavioral treatment) to achieve longer-term success. These findings also underscore the importance of emphasizing abstinence or near abstinence during the early treatment phase to promote stability. Given the urgent need to identify optimal treatment approaches for those who display early nonresponse to buprenorphine, the easily interpretable thresholds identified in this analysis may guide future research.

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Supplementary Material

Article Title: Identifying Optimal Thresholds for Early Opioid Use Frequency in Predicting Buprenorphine Outcomes

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Table 1** Missing Data in Study Variables (N=562)

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Supplementary Material

Missing data were imputed separately for each aim and each study to account for differences in methods (e.g., different follow-up lengths). For Aim 1, imputation models included opioid use frequency and craving scores (using a visual analog scale, included as it may inform missing values) in weeks 1-4 and the sustained opioid use variable. For Aim 2, imputation models included opioid use frequency in weeks 1-4, weekly data on opioid-free status after the first month of treatment, and the number of weeks participants were retained on buprenorphine retention (scored before imputation). All analyses were conducted in each imputed dataset (n=50 imputations) and pooled across imputations.

Information on missing data for each variable included in the analyses is reported below. Of note, missing data on opioid-free weeks indicates that participants were missing data on either self-reported opioid use or urine drug screens. No participants were missing data on sustained opioid use or buprenorphine retention outcomes, given that these incorporated missing data. Scoring of the early opioid use frequency variables (i.e., adding weeks 1-2, 1-3, and 1-4) and opioid free weeks was performed after imputation of missing data.

Supplementary Table 1. Missing Data in Study Variables (N=562)

Variable	N (%) of Missing Data
Early Opioid Use Frequency	
Week 1	5 (0.1%)
Week 2	9 (1.6%)
Week 3	21 (3.7%)
Week 4	24 (4.3%)
Opioid Free Weeks	
Week 5	60 (10.7%)
Week 6	67 (11.9%)
Week 7	75 (13.3%)
Week 8	88 (15.7%)
Week 9	98 (17.4%)
Week 10	102 (18.1%)
Week 11	107 (19.0%)
Week 12	116 (20.6%)