



Published in final edited form as:

Subst Use Addict J. 2025 April ; 46(2): 266–279. doi:10.1177/29767342241266038.

Association Between Length of Buprenorphine or Methadone Use and Nonprescribed Opioid Use Among Individuals with Opioid Use Disorder: A Cohort Study

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Abstract

Background: Opioid use disorder (OUD) affects millions of individuals each year in the United States. Patient retention in medications for opioid use disorder (MOUD) treatment is suboptimal. This study examines and quantifies the associations between each additional month of buprenorphine or methadone use and nonprescribed opioid use.

Methods: Data were obtained from an 18-month longitudinal, observational cohort study of patients (age ≥ 18 years) treated for OUD. Patients completed a baseline self-reported questionnaire between March 2018 and December 2019 and were asked to complete follow-up questionnaires at approximately 3-, 6-, 12-, and 18-months post-baseline until May 2021. Patients treated with buprenorphine or methadone, without taking other MOUD at least 12 months prior to

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Author Contributions

Authors XJ and GPG had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. XJ, GPG, JAD, JSR, LJD, MJE, JLL: concept and design. All authors: acquisition, analysis, or interpretation of data, and critical revision of the manuscript for important intellectual content. XJ: drafting of the manuscript. XJ, GPG, JAD, JSR, LJD, DT, MJE: statistical analysis. GPG, JAD, LJD, JLL: administrative, technical, or material support. GPG, JAD, JSR, LJD, JLL: supervision.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Compliance, Ethical Standards, and Ethical Approval

Institutional Review Board approval was not required.

Disclaimer

The views expressed herein are those of the authors and do not reflect the official policy or position of the Centers for Disease Control and Prevention, and RTI International.

Supplemental Material

Supplemental material for this article is available online at the *SAJ* website <http://journals.sagepub.com/doi/suppl/10.1177/29767342241266038>.

baseline, were included. Outcomes included past 30-day use of prescription opioids nonmedically, heroin, or illegally made fentanyl. A multivariable, multilevel regression model with a binomial distribution and a logit link was used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

Results: This study included 353 patients taking buprenorphine (mean [standard deviation, SD] age 39 [11] years; 226 [64%] female), and 785 patients taking methadone (mean [SD] age 42 [12] years; 392 [50%] female). Each additional month of MOUD treatment was associated with a 25% decrease in the odds of past 30-day nonprescribed opioid use for patients taking buprenorphine (aOR [95% CI] = 0.75 [0.68-0.83]), and a 17% decrease for patients taking methadone (aOR = 0.83 [0.79-0.87]). The COVID-19 pandemic (aOR = 9.29 [2.96-29.17]; aOR = 3.19 [1.74-5.86]) and MOUD adverse reaction experiences (aOR = 3.07 [1.11-8.48]; aOR = 2.51 [1.01-6.22]) were significantly associated with higher odds of nonprescribed opioid use among buprenorphine and methadone groups.

Conclusion: Among patients treated with buprenorphine or methadone, with each additional treatment month since baseline, those who continued with treatment appeared to be more likely to report 17% to 25% decreased odds of past 30-day nonprescribed opioid use. Our findings can be used by clinicians in the shared decision-making process with patients, emphasizing the value of sustained retention in MOUD.

Keywords

opioid use disorder; buprenorphine; methadone; nonprescribed opioid use; additional treatment month of Medications for Opioid Use Disorder

Introduction

Opioid use disorder (OUD) affects millions of individuals each year in the United States. In 2021, an estimated 5.6 million individuals aged ≥ 12 years had an OUD in the past year.¹ In addition, in 2021, an estimated 80 411 individuals died from an opioid-involved overdose, with 88% of those deaths involving synthetic opioids other than methadone (eg, illegally made fentanyl [IMF]).² Buprenorphine, methadone, and naltrexone—the 3 US Food and Drug Administration (FDA)-approved medications for treatment of OUD—are proven effective at treating OUD and decreasing nonprescribed opioid use and are among the evidence-based strategies for opioid overdose prevention.³

However, due to supply-side and demand-side barriers such as clinician availability, regulatory requirements, geographic accessibility, stigma, and cost,^{4,5} only around 1-in-5 individuals with OUD reported receiving medications for opioid use disorder (MOUD) in 2021.¹ Although no consensus exists for defining the optimal duration of MOUD,⁶ 6 months is a recommended minimum duration^{7,8} and longer retention (eg, at least 12^{9,10} or 15 months¹¹) in MOUD treatment is associated with improved outcomes (eg, reduced opioid prescriptions, overdose events, and all-cause mortality).^{6,11–16} However, patient retention in MOUD is suboptimal.^{16,17} A recent systematic review estimated that the pooled retention was 52% and 43% for sublingual buprenorphine and 56% and 47% for methadone

at 6 and 12 months, respectively.¹⁷ Effective strategies to increase MOUD retention are encouraged.¹⁷

Public health guideline in other medical fields, such as physical activity, highlight that “every minute counts” (eg, small amounts of aerobic activity provide some health benefits).¹⁸ This represents one strategy to encourage individuals to engage in physical activity and motivate them to gradually meet the recommended duration of physical activity.¹⁸ This strategy can also be applied to OUD treatment. Clinicians can build on patients’ incremental achievements in retaining MOUD during each small increment of treatment time to bolster patients’ self-confidence, aiding them in developing and believing in their ability to make healthy decisions.¹⁹ In fact, relatively small increases (each 2 month) in treatment duration are associated with reductions in the risk of overdose,⁶ and short treatment durations (<6 months) of methadone or buprenorphine could yield net mortality benefits.¹⁵ Quantifying the benefits of each additional month of MOUD treatment in patient outcomes could be imperative in informing clinical practice and designing public health interventions, thereby educating and motivating patients in retention.⁶

Given the rapid proliferation of IMF in the illicit drug markets, little research has examined the magnitude of the association between each additional month of MOUD therapy and nonprescribed opioid use including IMF, largely due to absence of questions related to IMF in traditional data collection.¹⁷ To further provide the benefits of each additional month of MOUD treatment and thus motivate patients to retain in MOUD, this study, utilizing recent longitudinal observational data, examines and quantifies the association between each additional month of buprenorphine or methadone use and nonprescribed opioid use including IMF while controlling for patient- and facility-level factors.

Methods

Study Population and Design

This is an observational cohort study, analyzing comprehensive 18-month longitudinal data funded by the US Centers for Disease Control and Prevention.^{20,21} Patients aged ≥ 18 years with OUD receiving treatment from 62 participating outpatient OUD treatment facilities across 16 states were referred to this study from March 2018 through December 2019.²¹ The specific OUD treatment a patient was receiving at the treatment facility when screened for study eligibility is referred to as the index treatment. The treatment facility where patients received their index treatment is referred to as the index facility. The original study protocol only recruited patients having started the index treatment at the index facility within the first 30 days. However, due to lower-than-expected patient recruitment numbers, the protocol was expanded with Institutional Review Board (IRB) approval to also include patients who were already receiving the index treatment for more than 30 days at the time of their enrollment into the study.²¹ This study was approved by the Office of Management and Budget and an independent IRB.

Participants screened eligible underwent an informed consent process before study enrollment (Supplemental Figure 1). Five-wave questionnaires were used to collect data from the enrolled patients between March 2018 and May 2021: a baseline (ie, study

enrollment) self-reported questionnaire, and 4 follow-up self-reported questionnaires at approximately 3-, 6-, 12-, and 18-months post-baseline. Patients were followed from baseline until they completed the 18-month post-baseline questionnaire, disenrolled (patients were retained in the study if they missed a follow-up questionnaire unless they rescinded their study enrollment) or the study period ended (May 31, 2021), whichever occurred first. In addition, since patients may end the index treatment or used other MOUD while on the same index treatment between the scheduled questionnaires, this study only followed the patients before the scheduled questionnaire time when patients reported stopping the index treatment or taking other MOUD while on the same index treatment, whichever came first.

The exposure in this study is index buprenorphine (oral, implantable, or injectable) or index methadone treatment since baseline. Patients reporting naltrexone or counseling-only as their index treatment were excluded due to a lack of power for statistical significance from low enrollment numbers. Patients were excluded if, at baseline, they reported (1) cessation of the index treatment, or (2) taking any MOUD other than their index treatment in the 12 months before baseline or during the period between the time index treatment began and baseline, whichever was longer (Supplemental Figure 2). “Buprenorphine” and “methadone” in subsequent text refers to the patient’s index treatment received at the index facility and not any subsequent MOUD received at other facilities.

All 5 patient questionnaires from baseline to 18-month post-baseline were used in this study and captured patient characteristics such as demographics (eg, race/ethnicity and sex), index treatment (buprenorphine or methadone), stopping the index treatment (Yes/No), and past 30-day substance use.

In addition to patient questionnaires, facility directors completed questionnaires when their index facility entered the study (ie, baseline) and again 18-months post-baseline. The baseline treatment facility questionnaire was used in this study to capture information on the facility’s primary healthcare focus, geographic region, and patient capacity. State policies related to MOUD access where the facilities were located were also included. (State policies contain state laws from all 50 states and Washington, D.C., enacted or in effect between 2018 and 2021. The laws contained demonstrate the scope of state laws that may affect access to MOUD.) Policy-related information was evaluated, created, and validated using 2 primary databases—LexisNexis and WestLaw. More information about recruitment protocols, data collection, and patient or treatment facility questionnaires has been documented elsewhere.²¹

Outcome Measures

The outcome of interest, collected throughout the 5-wave patient questionnaires, was past 30-day nonprescribed opioid use (Yes/No). Nonprescribed opioid use was defined as either nonmedical use of a prescription opioid, heroin use, or IMF use.

Covariates

Covariates were chosen based on their likelihood of having an association with nonprescribed opioid use, including patient-level covariates such as demographics, comorbidities, adverse childhood experiences (ACEs), number of nonprescribed opioids

used before baseline, treatment duration between the time index treatment began and baseline, treatment duration since baseline, as well as facility-level covariates such as facility region and patient capacity.^{22–26} State policy covariates included were “summative ranking of state legislation to reduce prior authorization barriers to MOUD” and “high State Opioid Response (SOR)/State Targeted Response to the Opioid Crisis (STR) grant funds going to state” (specific information about aforementioned covariates are in Supplemental Table 1).

Statistical Analysis

Descriptive statistics were used to summarize the patient demographics and index treatment facilities among patients taking buprenorphine or methadone, separately.

The data were hierarchical with 3 levels: level 1 included the responses within each of the baseline, 3-, 6-, 12-, and 18-month questionnaires; level 2 was the clustering of responses by patients; and level 3 was the clustering of patients by treatment facilities. A multivariable, multilevel logistic regression was conducted separately among patients taking buprenorphine or methadone to quantify the association between each additional month of treatment with buprenorphine or methadone and past 30-day nonprescribed opioid use since baseline. Each model included 2 random intercepts (patient and treatment facility) and a set of covariates described above. This approach accounts for within-patient correlations among the repeated measures from multiple waves of questionnaires and allows for variation among different patients and treatment facilities.²⁷

Each multilevel model used a binomial distribution with a logit link to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs; Supplemental Appendix 1). Model parameters were interpreted as subject-specific estimates instead of population averages. Intraclass correlations for treatment facility were examined to evaluate the variation in the outcome accounted for by the treatment facilities for each multilevel model.²⁷

The percentage of patients completing each questionnaire was 100% at baseline, 73% at 3 months, 71% at 6 months, 52% at 12 months, and 55% at 18 months postbaseline, respectively (Supplemental Table 2). Patient relocation, the COVID-19 pandemic, waning interest in the study without asking for disenrollment, or death may account for the loss-to-follow-up.²¹ Our multilevel models addressed missing data by maximum likelihood methods, which produced approximately unbiased estimates under the missing at random assumption after accounting for the covariates in the model.^{28–32}

Variance inflation factors were used to assess the multi-collinearity between the covariates.³³ No multicollinearity was detected in the final models. Two-tailed tests with a significance level of .05 were defined. Statistical analyses were conducted using SAS (version 9.4; SAS Institute).

Sensitivity Analyses

Sensitivity analyses were conducted to examine the robustness of the main results. First, we increased the time period for nonprescribed opioid use from past 30 days to past 90 days (this outcome also included nonmedical use of MOUD). Second, we reclassified patients who continued the same MOUD as the index treatment at another non-index facility

as continuing their index treatment. Third, we used a last-observation-carried-forward approach (for the third and fourth sensitivity analyses, we also used the last-observation-carried-forward approach to impute missing time-varying covariates for those who were lost-to-follow-up) to impute missing outcomes for those who were lost-to-follow-up; these individuals were assigned their last measured outcomes during subsequent rounds of follow-up. Fourth, we assumed a worst-case scenario for the outcomes that individuals who were lost-to-follow-up used the nonprescription opioids in the past 30 days and remained this outcome for all subsequent rounds.³⁴

Results

Patient Baseline Characteristics

Among 1974 enrolled adult patients with OUD, 1138 patients were identified as taking buprenorphine or methadone at baseline, with 353 (31%) patients taking buprenorphine (over 96% reported taking oral buprenorphine alone) and 785 (69%) patients taking methadone (Figure 1). At baseline, among patients treated with buprenorphine, middle-aged people (mean: 39 [standard deviation, SD: 11] years), females (64%), non-Hispanic White (72%), and those diagnosed with a mental illness (71%) accounted for the majority. Among patients treated with methadone, middle-aged people (mean: 42 [SD: 12] years), males (50%), non-Hispanic White (64%), and those diagnosed with a medical disease (69%) accounted for the majority. Of both groups, 86% had ACEs and around 50% had Medicaid only insurance coverage (Table 1).

The mean last MOUD treatment dose taken by patients at baseline was 11 (SD: 7) mg for buprenorphine and 93 (SD: 46) mg for methadone. The mean duration between the initiation of index treatment and baseline was 13 (SD: 24) and 25 (SD: 44) months for patients taking buprenorphine and methadone, respectively. The mean time patients continued their index treatment since baseline was 8 (SD: 7) months for buprenorphine and 10 (SD: 7) months for methadone (Table 1).

Index Treatment Facility Baseline Characteristics

Among index facilities treating patients with buprenorphine, 44% focused primarily on substance use services, 19% offered both mental health and substance use services, and 16% focused on general health services. Nearly three-fourths (74%) of these facilities were private nonprofit organizations and two-thirds (66%) provided trauma-informed care. In total, 65% of the index facilities were in the South.

Among index facilities treating patients with methadone, 93% focused primarily on substance use services, 54% were private for-profit organizations, and 54% provided-trauma informed care. One-third (33%) of the index facilities were located in the West. The mean reported distance for patients traveling to their index facility was 10 (SD: 13) and 8 (SD: 11) miles for buprenorphine and methadone, respectively (Table 2).

Association Between Additional Month of MOUD Treatment and Nonprescribed Opioid Use

After patient- and facility-level factors were controlled for, there appears to be an association between each additional month of MOUD treatment since baseline and decreased odds of past 30-day nonprescribed opioid use. Each additional month of MOUD treatment was associated with a 25% decrease in the odds of past 30-day nonprescribed opioid use for patients treated with buprenorphine (aOR = 0.75; 95% CI = 0.68-0.83) and a 17% decrease in the odds of past 30-day nonprescribed opioid use for patients treated with methadone (aOR = 0.83; 95% CI = 0.79-0.87; Table 3).

From baseline to 18-month follow-up, the cumulative percent of patients who reported discontinuation of their index treatment was 24% and 17% for patients taking buprenorphine and methadone, respectively.

Four sensitivity analyses corroborated our findings in the main analysis, indicating that past 30-day nonprescribed opioid use appeared to decrease with each additional treatment month for both MOUD treatments. The range for decreased odds of past 30-day nonprescribed opioid use with each additional treatment month appeared to be 15% to 30% for patients treated with buprenorphine, and 7% to 23% for patients treated with methadone across 4 sensitivity analyses (Supplemental Tables 3–6).

Other Factors Associated With Nonprescribed Opioid Use

For both buprenorphine and methadone groups, factors significantly associated with *decreased* odds (95% CI) of past 30-day nonprescribed opioid use included: Each additional month of MOUD treatment prior to baseline (aOR = 0.93 [0.89-0.97]; aOR = 0.97 [0.97-0.98]), having high social support (aOR = 0.48 [0.26-0.88]; aOR = 0.44 [0.28-0.70]) versus moderate social support, and compliance with MOUD treatment regimen (aOR = 0.29 [0.14-0.60]; aOR = 0.42 [0.24-0.74]). In addition, among individuals in the buprenorphine treatment group, being employed (aOR = 0.51 [0.27-0.95]), attending a self-help group (aOR = 0.45 [0.24-0.83]), and residing in a state receiving higher grant funding to combat the opioid crisis (aOR = 0.37 [0.16-0.84]) were associated with *decreased* odds of nonprescribed opioid use (Table 3).

Factors significantly associated with *increased* odds (95% CI) of past 30-day nonprescribed opioid use for individuals treated with either buprenorphine or methadone included: completing questionnaires during the COVID-19 pandemic (aOR = 9.29 [2.96-29.17]; aOR = 3.19 [1.74-5.86]) and a self-reported adverse reaction to MOUD (aOR = 3.07 [1.11-8.48]; aOR = 2.51 [1.01-6.22]). In addition, among those treated with buprenorphine, patients having suicidal thoughts in the past year (aOR = 2.46 [1.22-4.96]) were associated with *increased* odds of non-prescribed opioid use. While among individuals treated with methadone, those reporting nonmedical use of at least 2 types of nonprescribed opioids (aOR = 6.03 [1.39-26.15]) before baseline were associated with *increased* odds of nonprescribed opioid use (Table 3).

Discussion

In this study of patients with OUD who received outpatient buprenorphine or methadone treatment up to 18 months of follow-up since baseline, each additional month of MOUD treatment was associated with a 25% decrease in the odds of past 30-day nonprescribed opioid use for patients taking buprenorphine and a 17% decrease for patients taking methadone after accounting for patient- and facility-level factors.

The observed decrease in nonprescribed opioid use for both buprenorphine and methadone treatment is consistent with results from prior randomized controlled trials and retrospective studies.^{12,35,36} Our study further quantifies the benefits of each additional month of buprenorphine or methadone treatment, suggesting an association with reduced odds of nonprescribed opioid use, including IMF. Due to the high potency of IMF and unpredictable presence and concentrations in the illicit drug supply, individuals exposed to IMF are at high risk for fatal overdose.²⁴ Thus, continued access to MOUD and naloxone for patients with OUD remains essential and urgent public health interventions to reduce morbidity and mortality for individuals with OUD is needed.

While previous research suggests that retaining patients in MOUD for 6 months or longer is associated with better outcomes,^{6,9,11–16} achieving the recommended treatment duration may pose challenges in clinical practice. Our estimates could serve as encouragement for patients, indicating that they are likely to gain incremental benefits with each additional month of buprenorphine or methadone treatment up to 18 months, regardless of prior use of the same MOUD. Furthermore, a recent study found that each additional 2-month period of MOUD treatment was associated with a 10% reduction in opioid-related overdose among Medicaid enrollees.⁶ These findings can be used by clinicians in the shared decision-making process with patients and their family members, emphasizing the value of sustained retention in MOUD. Policy makers can also use this information to carefully consider policies that impose limits on MOUD treatment duration.^{6,37} Future research is needed to investigate whether informing patients that “every month of MOUD treatment counts” could result in better retention outcomes compared to a strategy that advises patients to meet a specific duration threshold.

Consistent with other studies,^{12,17,38,39} we found that there was increasing dropout from index treatment over the 18-month follow-up period for both groups (only around 8% of patients discontinuing the index treatment were involuntarily discharged from the index facility due to continuing substance use, which could rule out the possibility of reversal causality), especially for patients taking buprenorphine. A growing body of research has demonstrated that clinical and social factors such as lower daily dosage, higher MOUD cost-sharing, and longer distance from treatment sites can affect treatment retention.^{40,41} In addition, discontinuation of MOUD increases the risk of overdose death in patients with OUD, especially in the first month following discontinuation.¹⁶ These findings underscore the importance of engaging and retaining patients in MOUD treatment. Efforts to increase treatment duration could include use of mobile medical applications, contingency management, telehealth services, transportation support, public health educational campaigns, screening for and treating co-occurring mental illness,

innovative evidence-based state collaborative care models, and changes in benefit design for MOUD cost coverage.^{11,13,41–46} Additional research is needed to investigate and develop effective interventions to improve MOUD retention.

Buprenorphine and methadone served different patient populations with OUD in our study, we thus did not compare the effectiveness of the 2 treatments in reducing nonprescribed opioid use directly. Of note, several studies have compared these 2 treatments directly with mixed results.^{12,17,35,36,47} One recent systemic review and 2 trials in real-world clinical settings found buprenorphine to be more effective in reducing nonprescribed opioid use compared to methadone.^{12,17,47} However, a randomized controlled trial and an observational study found methadone was associated with less opioid use than buprenorphine.^{35,36} Differences in results among these studies could be due to different treatment settings, follow-up periods, or outcomes measured.

This study also underscores the association between some patient-level characteristics and nonprescribed opioid use. For example, we found that each additional month of MOUD treatment before baseline was associated with decreased odds of nonprescribed opioid use. Our finding underscores the importance of continuing or reinitiating MOUD treatment whenever and wherever patients with OUD are ready to do so.⁴⁸ Patients experiencing an adverse reaction to MOUD appeared to be more likely to report nonprescribed opioid use. Careful medication management by healthcare professionals may limit adverse medication reactions and prevent return to nonprescribed opioid use.⁴⁹

Patients completing questionnaires during the COVID-19 pandemic were associated with increased odds of nonprescribed opioid use. This is consistent with early evidence attributed to reduced social support, increased psychological distress, and decreased access to, or disruption of, treatment and harm reduction services.^{25,50–52} Of note, COVID-19 and the ongoing opioid overdose crisis have led to rapid innovations in OUD services with a reduction in barriers for evidence-based MOUD and harm reduction services such as extended methadone take-home flexibility and reimbursement for telehealth behavioral health services.^{53–55}

Despite the many benefits of the research, this study is subject to limitations. First, this observational study cannot establish causality and unmeasured confounders may have affected our results. For example, dosage of the index treatment across the observation period was not available. However, we had information about the last dosage of MOUD patients used at baseline, 12 months, and 18 months. There was no marked variation in the mean dosage for both treatments at these 3 time-points. Therefore, differential MOUD dose was unlikely to have been a significant confounder in this analysis. Second, the study may be subject to nonresponse bias.^{21,56} Nevertheless, we conducted sensitivity analyses to impute missing values, exploring potential extremes for our results. These sensitivity analyses revealed a consistent association between each additional month of buprenorphine or methadone use and reduced odds of nonprescribed opioid use, suggesting the robustness of our main findings.³⁴ Further investigation is needed to better understand individuals who do not respond to the patient questionnaires. In addition, more in-depth statistical analyses under different missingness mechanisms are necessary to address nonresponse bias and

confirm the robustness of our results.^{30,31} Third, we were unable to measure outcomes at the time index treatment ended. We may underestimate the benefit of each additional treatment month associated with the nonprescribed opioid use outcome. Fourth, self-reported data are subject to potential recall biases. Fifth, our results may not be generalizable to all patients with OUD, particularly patients aged <18 years, or patients treated at rural outpatient treatment facilities with limited treatment services.²¹ Sixth, to increase patient enrollment numbers, the original study protocol recruiting patients within the first 30 days of their index treatment was removed.²¹ Thus, some patients were likely more engaged in their MOUD treatment while enrolled. We controlled for the treatment time between the initiation of the index treatment and baseline to reduce survivorship bias. Future research focusing on patients who initiated the MOUD is needed to confirm our results. Seventh, we only focused on nonprescribed opioid use outcome which may not reflect patients' own goals for their treatment.⁴⁸

Conclusion

Among patients undergoing outpatient OUD treatment with buprenorphine or methadone up to 18 months following baseline, those who continued treatment for each additional month appeared to be more likely to report 17% to 25% decreased odds of past 30-day nonprescribed opioid use including IMF. Continued efforts at the patient, clinician, health system, and practice levels are needed to improve MOUD treatment retention. This work also underscores several key factors associated with nonprescribed opioid use that can help inform future prevention efforts to prevent nonprescribed opioid use. Our findings can be used by clinicians, patients, and their family members to improve MOUD retention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Thank you to Bradley B. Biggers, MS (CDC) for his consultations on the dataset, Arnie Aldridge, PhD (RTI) and Camille Gourdet, JD (RTI) for creating the policy variables, Dorothy Wu, JD (RTI) and Harley Rohloff, PhD (RTI) for helping with data cleaning, Kun Zhang, PhD (CDC), Marziyeh Omid, MS (CDC), and Phuong N. Pham, PhD (UF) for their consultations on the study design, as well as Zachary Illg, DO (CDC) and Matthew Dernbach, MD (CDC) for providing their clinical expertise.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was produced under contract number HHSD 20002013M53964B with Centers for Disease Control and Prevention and US Department of Health and Human Services between 2016 and 2021. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Highlights

- Patients who continued with buprenorphine or methadone treatment for each additional month were more likely to report 17% to 25% decreased odds of past 30-day nonprescribed opioid use.
- COVID-19 pandemic was associated with higher odds of past 30-day nonprescribed opioid use.
- Our findings can be used by clinicians in the shared decision-making process with patients and their family members, emphasizing the value of sustained retention in medications for opioid use disorder.

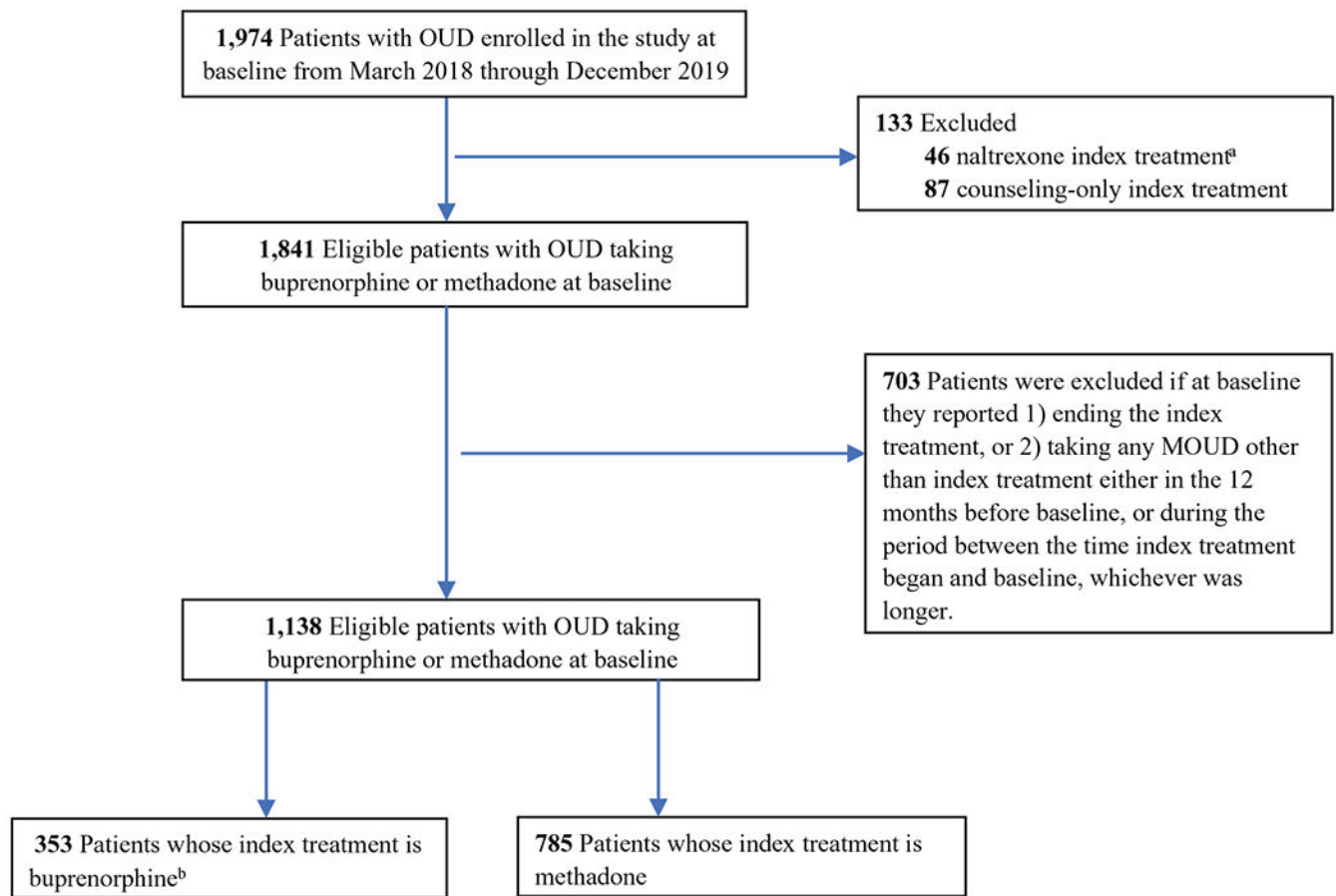


Figure 1.

Flow of patients in a study of the association between additional month of buprenorphine or methadone use and nonprescribed opioid use.

Abbreviation: OUD, opioid use disorder; MOUD, medications for opioid use disorder.

^aThe specific treatment for OUD that a patient reported receiving at the study treatment facility when screened is referred to as the index treatment; ^bOver 96% reported taking oral buprenorphine alone as the index buprenorphine treatment. Less than 4% reported taking both oral and implantable/injectable buprenorphine as the index buprenorphine treatment or did not report the type of the index buprenorphine (The authors did not report the numbers <11 owing to the Centers for Medicare and Medicaid Services cell size suppression policy.)

Table 1.

Baseline Patient Characteristics for Patients Who Received Buprenorphine or Methadone as MOUD.

Characteristics	Buprenorphine (N = 353)	Methadone (N = 785)
Age, mean (SD)	39.2 (11.2)	41.5 (11.7)
Age (years)		
18-24	22 (6.2%)	27 (3.4%)
25-34	117 (33.1%)	244 (31.1%)
35-44	110 (31.2%)	210 (26.8%)
45-54	61 (17.3%)	175 (22.3%)
≥55	43 (12.2%)	129 (16.4%)
Sex		
Male	127 (36.0%)	393 (50.1%)
Female	226 (64.0%)	392 (49.9%)
Race/ethnicity ^a		
White only, non-Hispanic	251 (71.7%)	496 (64.3%)
Black only, non-Hispanic	24 (6.9%)	97 (12.6%)
Other or mixed race, non-Hispanic	17 (4.9%)	43 (5.6%)
Hispanic, any race	58 (16.6%)	135 (17.5%)
Currently employed or self-employed		
Yes	108 (30.6%)	198 (25.2%)
No	245 (69.4%)	587 (74.8%)
Insurance type ^b		
Private	37 (10.5%)	56 (7.2%)
Medicare only	45 (12.8%)	104 (13.4%)
Medicaid only	165 (46.9%)	393 (50.6%)
Other ^c	36 (10.2%)	109 (14.1%)
No insurance	69 (19.6%)	114 (14.7%)
Level of social support ^d		
High	222 (62.9%)	454 (57.8%)
Moderate	111 (31.4%)	272 (34.7%)
Low	20 (5.7%)	59 (7.5%)

Characteristics	Buprenorphine (N = 353)	Methadone (N = 785)
Had one or more adverse childhood experience ^e		
Yes	305 (86.4%)	673 (85.7%)
No	48 (13.6%)	112 (14.3%)
Ever diagnosed with a mental illness ^f		
Yes	251 (71.1%)	461 (58.7%)
No	102 (28.9%)	324 (41.3%)
Ever diagnosed with a medical disease ^g		
Yes	233 (66.8%)	530 (68.6%)
No	116 (33.2%)	243 (31.4%)
Experienced an adverse reaction to MOUD (for the current or most recent treatment)		
Yes	24 (6.8%)	24 (3.1%)
No	329 (93.2%)	761 (96.9%)
Number of nonprescribed opioid types before baseline ^h		
None ⁱ	<11 (3.1%) ⁱ	26 (3.3%)
One	>67 (19.0%) ^j	150 (19.1%)
Two or more	275 (77.9%)	609 (77.6%)
Use of other substances before baseline		
Prescription stimulants nonmedically	172 (48.7%)	311 (39.6%)
Prescription sedatives nonmedically	238 (67.4%)	445 (56.7%)
Neuropathics nonmedically (eg, gabapentin, pregabalin)	120 (34.0%)	194 (24.7%)
Methamphetamine/crank	168 (47.6%)	308 (39.2%)
Alcohol	261 (73.9%)	520 (66.2%)
Other services received while in index treatment		
Counseling ^k	331 (93.8%)	703 (89.6%)
Peer-to-peer recovery support services	98 (27.8%)	151 (19.2%)
Detoxification services	82 (23.2%)	92 (11.7%)
Laboratory drug testing/urine testing	242 (68.6%)	522 (66.5%)
Medical services (eg, physical examinations, medication)	184 (52.1%)	281 (35.8%)
Attended a self-help group in the past 90 days	164 (46.5%)	244 (31.1%)
Emergency department or hospital stay related to opioids in the past 90 days ^l	39 (11.1%)	45 (5.7%)

Characteristics	Buprenorphine (N = 353)	Methadone (N = 785)
Visited a primary care clinician in the past 90 days ^m	195 (55.4%)	377 (48.1%)
Patients' attitudes		
Patients choose the treatment facility by themselves to get their index treatment ⁿ	233 (66.0%)	602 (76.7%)
Tried to stop using opioids voluntarily ^o	290 (82.9%)	636 (81.4%)
Suicidal thoughts in the past 12 months ^p	47 (13.4%)	69 (8.9%)
Compliance with MOUD treatment regimen ^q	310 (87.8%)	679 (86.5%)
Mean HRQoL based on the EQ-5D-5L health utility values (SD)	0.7 (0.2)	0.7 (0.2)
Mean treatment dose the last time patients took this treatment, milligrams (SD) ^r	11.0 (6.7)	93.3 (45.9)
Mean treatment duration between initiation of index treatment and baseline, months (SD)	12.8 (23.6)	25.3 (44.1)
Mean number of months patients were enrolled (SD) ^s	11.1 (7.1)	11.2 (6.6)
Mean number of months patients continued their index treatment since baseline (SD)	7.9 (6.9)	9.5 (6.8)

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; HRQoL, health-related quality of life (ranges from 0 to 1); IMF, illegally made fentanyl; MOUD, Medications for Opioid Use Disorder; SD, standard deviation.

^aThere are 17 nonresponses to this item and were the records excluded from the model;

^bThere are 10 nonresponses to this item and were the records excluded from the model;

^cInclude Medicaid/Medicare dual eligibility, and Veterans Administration-provided insurance;

^dSocial support: patients reported that they get the emotional help and support from family, friends, or other special persons;

^eACE: patients reported that before they were 18 years of age, they lived with someone who was depressed, mentally ill, or suicidal, or who was a problem drinker or alcoholic, or who used illegal street drugs or prescription medications nonmedically, or who served time or was sentenced to serve time in a prison, jail, or other correctional facility, or who at least 5 years older than the responders or an adult, ever touched the responders sexually, tried to make the responders touch them sexually, or forced the responders to have sex, or lived with those who at home ever slapped, hit, kicked, punched, beat, or physically hurt each other or the responders more than once, or lived with those who ever swore at responders, insulted responders, or put responders down more than once, or responders reported that adults in their household never or rarely tried hard to make sure the responders' basic needs were met, or made the responders feel safe and protected;

^fMental illness includes major depression/clinical depression, bi-polar disorder/mania/manic depression, dysthymia, generalized anxiety disorder, phobia (eg, specific phobias like spiders or general phobias like agoraphobia), posttraumatic stress disorder/PTSD, panic disorder, conduct disorder (before age 18), personality disorder (eg, borderline personality disorder, anti-social personality disorder), intermittent explosive disorder, ADHD, obsessive-compulsive disorder, eating disorder (eg, anorexia nervosa, binge eating disorder), and other mental health condition;

^gThere are 16 missingness. Medical disease includes anemia, arthritis, asthma, cancer, cirrhosis of the liver, diabetes type I, diabetes type II, fibromyalgia, heart disease, hepatitis C, high blood pressure (hypertension), HIV/AIDS, osteoporosis, pancreatitis, pneumonia, sexually transmitted disease (eg, chlamydia, herpes, syphilis, gonorrhea), sleep apnea, stroke, tuberculosis, and ulcer(s);

^hNonprescribed opioid use includes nonmedical prescription opioid use, nonmedical MOUD use, heroin use, and IMF use;

ⁱNone: Patients did not report using prescription opioids nonmedically, MOUD nonmedically, heroin, or IMF before baseline;

- j* The authors did not report the numbers <11 due to the Centers for Medicare & Medicaid Services cell size suppression policy;
- k* Counseling includes individual counseling, group counseling, and other behavioral therapy/counseling while in index treatment;
- l* Emergency department or hospital stay related to opioids: patients reported that they visited the emergency department due to injuries or conditions resulting from opioid addiction, or they reported that they spent nights in hospitals which were related to injuries or conditions resulting from opioid addiction;
- m* There are 2 nonresponses to this item and were the records excluded from the model;
- n* The specific treatment for OUD that a patient reported receiving at the study treatment facility when screened is referred to as the index treatment and was not randomly assigned;
- o* There are 7 nonresponses to this item and were the records excluded from the model;
- p* There are 8 nonresponses to this item and were the records excluded from the model;
- q* This means that patients reported “yes” to “Do/did you usually take opioid treatment medication as directed by your doctor (for the current or most recent treatment)” in the questionnaire;
- r* Among the 353 persons who used buprenorphine, 312 reported the dose for oral buprenorphine they took at the last time is 11.0 (6.7) mg; 10 reported the dose for implant/injection buprenorphine they took at the last time is 13.4 (5.1) mg. Among the 785 persons who used methadone, 692 reported the dose for methadone they took at the last time is 93.3 (45.9) mg;
- s* This measures the follow-up time when patients were enrolled in the study since baseline before the censoring criteria was applied.

Table 2.

Baseline Characteristics for Index Treatment Facilities Where Patients Received Buprenorphine or Methadone as MOUD.^a

Characteristics	Buprenorphine (N = 353)	Methadone (N = 785)
The ratio of treated patients with OUD per 10 staff at the treatment facility (mean + SD) ^b	1.0 (0.9)	3.4 (2.3)
Treatment facility focus		
Substance use	155 (43.9%)	727 (92.6%)
Mental health and substance use	68 (19.3%)	>47 (6.0%)
General health	56 (15.9%)	<11 (1.4%) ^c
Other	74 (21.0%)	<11 (1.4%) ^c
Ownership type of the treatment facility		
Private for-profit	59 (16.7%)	422 (53.8%)
Private nonprofit	262 (74.2%)	270 (34.4%)
Government owned	32 (9.1%)	93 (11.9%)
Treatment facility provides trauma-informed care		
Yes	234 (66.3%)	427 (54.4%)
No	119 (33.7%)	358 (45.6%)
Treatment facility region		
Northeast	52 (14.7%)	130 (16.6%)
Midwest	35 (9.9%)	183 (23.3%)
South	230 (65.2%)	210 (26.8%)
West	36 (10.2%)	262 (33.4%)
Patient capacity (ie, number of patients with OUD receiving treatment at the treatment facility)		
≤250	218 (61.8%)	71 (9.0%)
251-450	62 (17.6%)	273 (34.8%)
≥451	73 (20.7%)	441 (56.2%)
Approximate miles to treatment facility for patients (mean + SD)	9.5 (12.8)	8.3 (10.9)
State policies		
Summative ranking of state legislation to reduce prior authorization barriers to MOUD: mean (SD) ^d	2.2 (2.1)	1.7 (2.3)
High SOR/STR grant funds per month per capita (100 k) (2017) going to state (greater than or equal to \$19 137) ^e	175 (49.6%)	176 (22.4%)

Source: [USAspending.gov](https://www.usaspending.gov).

Abbreviations: MOUD, medications for opioid use disorder; SD, standard deviation; SOR, state opioid response; STR, state targeted response.

^aThe treatment facility where patients received their index treatment is referred to as the index facility;

^bStaff includes medical staff and counseling staff;

^cThe authors did not report the numbers <11 due to the Centers for Medicare & Medicaid Services cell size suppression policy;

^dSummative ranking of state legislation to reduce prior authorization barriers to MOUD (0-8): 0 = no legislation, 8 = legislation affecting all MOUD medications, within all classes and both Medicaid and private insurance;

^eSOR/STR to the Opioid Crisis grant funds.

Table 3.

Adjusted Odds Ratios (95% CI) for Past 30-Day Nonprescribed Opioid Use Among Patients Taking Buprenorphine or Methadone Controlling for Patient-Level and Facility-Level Characteristics.^a

Parameters	Adjusted odds ratio among patients taking buprenorphine	Adjusted odds ratio among patients taking methadone
Time in study		
Treatment months since baseline	0.75 (0.68-0.83)	0.83 (0.79-0.87)
Treatment duration between the time when index treatment began and baseline (month)	0.93 (0.89-0.97)	0.97 (0.97-0.98)
Any patient-questionnaire completed during the COVID-19 pandemic (after March 1, 2020)		
Yes	9.29 (2.96-29.17)	3.19 (1.74-5.86)
No	Reference	Reference
Age (years)		
18-24	1.20 (0.31-4.64)	2.23 (0.64-7.75)
25-34	1.32 (0.49-3.53)	1.85 (0.91-3.75)
35-44	0.96 (0.36-2.57)	1.29 (0.64-2.58)
45-54	2.15 (0.76-6.11)	2.14 (1.08-4.23)
≥55	Reference	Reference
Sex		
Male	0.87 (0.46-1.62)	1.25 (0.81-1.93)
Female	Reference	Reference
Race/ethnicity		
Hispanic, any race	2.08 (0.79-5.46)	0.78 (0.42-1.45)
Black only, non-Hispanic	1.90 (0.67-5.39)	2.01 (1.01-4.03)
Other or mixed race, non-Hispanic	0.82 (0.24-2.78)	1.56 (0.63-3.86)
White only, non-Hispanic	Reference	Reference
Currently employed or self-employed		
Yes	0.51 (0.27-0.95)	0.81 (0.52-1.24)
No	Reference	Reference
Insurance type		
Private	4.43 (1.18-16.61)	0.72 (0.26-1.96)
Medicare only	0.89 (0.22-3.66)	1.24 (0.53-2.88)
Medicaid only	1.44 (0.56-3.72)	1.32 (0.66-2.62)

Parameters	Adjusted odds ratio among patients taking buprenorphine	Adjusted odds ratio among patients taking methadone
Other ^b	0.84 (0.30-2.34)	1.46 (0.62-3.42)
No insurance	Reference	Reference
Level of social support ^c		
High	0.48 (0.26-0.88)	0.44 (0.28-0.70)
Low	0.91 (0.31-2.67)	0.88 (0.36-2.11)
Moderate	Reference	Reference
Had one or more adverse childhood experience ^d		
Yes	1.83 (0.75-4.46)	1.82 (0.96-3.48)
No	Reference	Reference
Ever diagnosed with a mental illness ^e		
Yes	1.24 (0.68-2.28)	1.07 (0.66-1.74)
No	Reference	Reference
Ever diagnosed with a medical disease ^f		
Yes	1.28 (0.72-2.29)	0.87 (0.55-1.38)
No	Reference	Reference
Experienced an adverse reaction to MOUD (for the current or most recent treatment)		
Yes	3.07 (1.11-8.48)	2.51 (1.01-6.22)
No	Reference	Reference
Number of nonprescribed opioid types before baseline ^g		
One	NA ^h	4.29 (0.96-19.18)
Two or more	NA ^h	6.03 (1.39-26.15)
None ⁱ	Reference	Reference
Ever used other substances before baseline		
Prescription stimulants nonmedically	0.93 (0.48-1.80)	1.37 (0.80-2.35)
Prescription sedatives nonmedically	1.44 (0.72-2.86)	1.82 (1.05-3.12)
Neuropathics nonmedically (eg, gabapentin, pregabalin)	1.87 (0.97-3.62)	0.96 (0.56-1.65)
Methamphetamine/crank	0.98 (0.51-1.88)	1.35 (0.79-2.31)
Alcohol	0.80 (0.42-1.52)	0.94 (0.57-1.54)
Other services received while in index treatment		

Parameters	Adjusted odds ratio among patients taking buprenorphine	Adjusted odds ratio among patients taking methadone
Counseling ⁱ	0.40 (0.11-1.41)	0.65 (0.32-1.34)
Peer-to-peer recovery support services	0.70 (0.36-1.36)	1.03 (0.58-1.84)
Detoxification services	0.85 (0.43-1.72)	1.14 (0.56-2.32)
Medical services (eg, physical exams, medication)	0.94 (0.54-1.64)	0.61 (0.37-1.03)
Attended a self-help group in the past 90 days	0.45 (0.24-0.83)	0.81 (0.51-1.27)
Emergency department or hospital stay related to opioids in the past 90 days ^k	2.26 (1.05-4.85)	2.27 (0.93-5.55)
Visited a primary care clinician in the past 90 days	0.54 (0.30-0.95)	0.93 (0.59-1.45)
Patient's travel burden		
Approximate miles to index treatment facility for patients	0.99 (0.96-1.02)	1.01 (0.99-1.03)
Patients' attitudes		
Patients choose the treatment facility by themselves to get their index treatment	0.65 (0.37-1.15)	0.74 (0.45-1.23)
Tried to stop using opioids voluntarily	1.14 (0.47-2.74)	2.09 (1.13-3.86)
Suicidal thoughts in the past 12 months	2.46 (1.22-4.96)	1.34 (0.65-2.78)
Compliance with MOUD treatment regimen ^l	0.29 (0.14-0.60)	0.42 (0.24-0.74)
Site-level characteristics		
The ratio of treated patients with OUD per 10 staff at the treatment facility ^m	1.21 (0.57-2.54)	0.96 (0.83-1.11)
Treatment facility focus		
Substance use	2.77 (0.51-14.88)	NA ⁿ
Mental health and substance use	3.95 (0.65-23.98)	NA ⁿ
General health	0.53 (0.12-2.33)	NA ⁿ
Other	Reference	Reference
Ownership type of the treatment facility		
Private nonprofit	2.30 (0.62-8.45)	1.24 (0.57-2.71)
Government owned	1.64 (0.26-10.49)	1.30 (0.44-3.84)
Private for-profit	Reference	Reference
Treatment facility offers trauma interventions		
Yes	1.03 (0.20-5.38)	0.78 (0.41-1.46)
No	Reference	Reference
Index treatment facility region		
Northeast	0.11 (0.02-0.74)	0.78 (0.29-2.14)

Parameters	Adjusted odds ratio among patients taking buprenorphine	Adjusted odds ratio among patients taking methadone
Midwest	0.14 (0.02-1.25)	5.14 (2.22-11.88)
South	0.14 (0.02-1.09)	0.42 (0.19-0.93)
West	Reference	Reference
Patient capacity (ie, number of patients with OUD receiving treatment at the treatment facility)		
251-450 patients	3.57 (0.51-24.98)	3.62 (1.28-10.25)
≥451 patients	0.99 (0.08-11.91)	1.78 (0.61-5.14)
≤250 patients	Reference	Reference
State policies		
Summative ranking of state legislation to reduce prior authorization barriers to MOUD ^a	0.93 (0.77-1.12)	0.92 (0.81-1.04)
High SOR/STR grant funds per month per capita (100 k; 2017) going to state (greater than or equal to \$19 137) ^p	0.37 (0.16-0.84)	1.37 (0.74-2.55)

Abbreviations: ADHD, attention-deficit hyperactivity disorder; CI, confidence intervals; IMF, illegally made fentanyl; MOUD, medications for OUD; SOR, state opioid response; STR, state targeted response to the opioid crisis.

^aN = 1136 unique patients at baseline rather than 1138 due to missing data for the outcome (N = 2); N = 3396 records from baseline to 18 months (ie, 940 records for patients taking buprenorphine and 2456 records for patients taking methadone). Among patients taking buprenorphine or methadone, the intraclass correlation for the treatment facility-level random intercept was 3.20E-07 (*P* = .5), indicating that approximately 0% of the variability in the probability of nonprescribed opioid use outcome is accounted for by the treatment facility for both groups, leaving 100% of the variability to be accounted for by the patients or other unknown factors. The output also indicates that there is not a statistically significant amount of variability in the log odds of nonprescribed opioid use outcome between the treatment facilities in our sample. Nonprescribed opioid use is defined as either nonmedical prescription opioid use, heroin use, or IMF use;

^bOther includes Medicaid/Medicare dual eligibility, Veterans Administration-provided insurance, and other insurances;

^cSocial support: patients reported that they get the emotional help and support from family, friends, or other special persons;

^dAdverse childhood experience: patients reported that before they were 18 years of age, they lived with someone who was depressed, mentally ill, or suicidal, or who was a problem drinker or alcoholic, or who used illegal street drugs or prescription medications nonmedically, or who served time or was sentenced to serve time in a prison, jail, or other correctional facility, or who at least 5 years older than the responders or an adult, ever touched the responders sexually, tried to make the responders touch them sexually, or forced the responders to have sex, or lived with those who at home ever slapped, hit, kicked, punched, beat, or physically hurt each other or the responders more than once, or lived with those who ever swore at responders, insulted responders, or put responders down more than once, or responders reported that adults in their household never or rarely tried hard to make sure the responders' basic needs were met, or made the responders feel safe and protected;

^eMental illness includes major depression/clinical depression, bi-polar disorder/mania/ manic depression, dysthymia, generalized anxiety disorder, phobia (eg, specific phobias like spiders or general phobias like agoraphobia), posttraumatic stress disorder/PTSD, panic disorder, conduct disorder (before age 18), personality disorder (eg, borderline personality disorder, anti-social personality disorder), intermittent explosive disorder, ADHD, obsessive-compulsive disorder, eating disorder (eg, anorexia nervosa, binge eating disorder), and other mental health condition;

^fThere are 51 nonresponses to this item and were the records excluded from the model. Medical disease includes anemia, arthritis, asthma, cancer, cirrhosis of the liver, diabetes type I, diabetes type II, fibromyalgia, heart disease, hepatitis C, high blood pressure (hypertension), HIV/AIDS, osteoporosis, pancreatitis, pneumonia, sexually transmitted disease (eg, chlamydia, herpes, syphilis, gonorrhea), sleep apnea, stroke, tuberculosis, and ulcer(s);

^gNonprescribed opioid includes nonmedical prescription opioids use, nonmedical MOUD use, heroin use, and IMF use;

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- q N/A: Due to the small sample size of the reference group, the estimate was large, so the result is not shown. Each 95% CI result include one;
- i None: Patients did not report using prescription opioid nonmedically, MOUD nonmedically, heroin, or IMF before baseline;
- j Counseling includes individual counseling, group counseling, and other behavioral therapy/counseling while in index treatment;
- k Emergency department or hospital stay related to opioids; patients reported that they visited the emergency department due to injuries or conditions resulting from opioid addiction, or they reported that they spent nights in hospitals which were related to injuries or conditions resulting from opioid addiction;
- l This means that patients reported “yes” to “Do/did you usually take opioid treatment medication as directed by your doctor (for the current or most recent treatment)” in the questionnaire;
- m Staff includes medical staff and counseling staff;
- n N/A: Due to the small sample size of the reference group, the estimate was large, so the result is not shown. Each 95% CI result include one;
- o Summative ranking of state legislation to reduce prior authorization barriers to MOUD (0-8); 0 = no legislation, 8 = legislation affecting all MOUD medications, within all classes, and both Medicaid and private insurance;
- p The reference group is SOR/STR grant funds per month per capita (100 k) less than \$19 137.