Retrospective Study

From Chronic Opioids for Pain to Microgram Buprenorphine: Key Factors in an Increasingly Recommended Transition

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Background: Guidelines on the use of opioids in chronic pain management increasingly recommend consideration of buprenorphine for patients on long-term full agonist opioid therapy. Published strategies for patients' transitions to buprenorphine vary widely in terms of study design, dose, formulation, and timing of buprenorphine initiation. A further limitation in informing an ideal transition strategy is the paucity of data describing factors that influence the likelihood of a successful transition.

Objectives: We sought to describe factors that influenced the likelihood of a successful transition to buprenorphine.

Study Design: Retrospective cohort study.

Setting: This research used data from the national Corporate Data Warehouse of the Veterans Health Administration

Methods: We reviewed the Veterans Affairs Corporate Data Warehouse for information concerning patients who had outpatient opioid prescriptions and had received microgram-strength buprenorphine. With this information in mind, we examined the factors associated with a successful transition to buprenorphine.

Results: We identified significant reductions in the number of patients prescribed full agonist opioids and in the total dose of opioids prescribed after buprenorphine exposure, with the largest effect observed in patients who continued using buprenorphine. While the potency and dose of baseline opioids were not predictive of the continued use of buprenorphine, higher opioid doses were associated with a decreased likelihood of continuation. Although factors correlating with patient support were associated with buprenorphine continuation, factors correlating with reduced support were associated with lower odds of continued buprenorphine use.

Limitations: Limitations inherent to large-scale observational studies are present, including imperfect data quality/ integrity, incomplete data, and the use of stop codes and CPT codes to determine the nature of a clinical encounter. The dataset is limited to the information collected, which excludes other factors likely associated with the outcomes. We used the continuous prescription of buprenorphine as a surrogate marker of a successful transition. Given the retrospective nature of the study, we are unable to determine if buprenorphine exposure is causally related to reduced opioid use. The population served by the Veterans Health Administration is not representative of other populations, and the results of this study may not generalize to other patient populations.

Conclusions: Our findings support the recommendation to trial buprenorphine in patients receiving chronic opioid therapy. This study's results also suggest that patient factors and shared decision-making are more important predictors of success than are the pharmacologic properties, potency, or dose of pre-rotation opioid exposure.

Key words: Buprenorphine, chronic pain, chronic opioid therapy, long-term opioid therapy, opioid rotation, opioid weaning, opioid use disorder

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The 2016 Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain focused on the effectiveness of chronic opioid therapy (COT) (1). The document identified no evidence that COT resulted in long-term benefits to patients' levels of pain and functioning. On the contrary, the official guideline found evidence of harm, including dose-dependent increases to the risks of opioid misuse, overdose, cardiovascular events, and road trauma. The CDC's recommendations included careful initial and subsequent consideration of the risks and benefits of opioid therapy, such as reviewing prescriptions of controlled substances, the prioritization of immediate-release formulations in the lowest effective doses, testing urine samples for drugs, avoiding the prescription of benzodiazepines, and offering buprenorphine to patients with opioid use disorder (OUD). If, at reevaluation, the benefits did not outweigh the harms, clinicians should "work with patients to taper opioids to lower dosages or to taper and discontinue opioids" (1) in addition to optimizing other therapies.

A 2022 update to the CDC guideline maintained the recommendations regarding the use of opioids for chronic pain and emphasized the importance of making patient-centered decisions (2). This focus arose partly due to misapplications of the 2016 guideline that could include rapid tapering, abrupt discontinuation, patient abandonment, and other associated harms (3-5). The updated guidance on tapering includes a recommendation to consider buprenorphine for patients who have continued to use high doses of opioids without seeing benefits, who have been unable to taper, and who do not meet the criteria for OUD. The authors describe a "traditional" approach wherein buprenorphine is initiated only after the onset of withdrawal symptoms and a "low dose initiation" without waiting for withdrawal.

Another 2022 guideline on the use of opioids in chronic pain, from a U.S. Department of Veterans Affairs (VA) and Defense work group, makes a new recommendation to consider buprenorphine instead of full agonist opioids (FAO) for patients prescribed daily opioids (6). The authors cite buprenorphine's superior safety profile, specifically "lower risk for overdose and misuse." Importantly, this recommendation is to consider buprenorphine in lieu of FAO, not to facilitate a challenging taper of FAO.

Notably, the 2022 CDC guideline does not apply to pain related to malignancy, sickle cell disease, or palliative care; opioids remain an accepted analgesic modality in populations with these conditions. Regardless of the etiology, there are reasons to be enthusiastic about buprenorphine's potential in pain management. Infantino et al (7) review the unique pharmacology of buprenorphine and its inherent advantages over other opioids in chronic pain management. These researchers cite buprenorphine's inherent multimodal opioid pharmacology (partial mu agonism, opioid-like receptor 1 agonism, and kappa and delta antagonism), anti-hyperalgesic properties that may result from voltage-gated sodium channel blockades, mitigation of opioid-induced dynorphin upregulation, and biased agonist profile resulting in more G protein-coupled receptor activation and less β-arrestin recruitment mitigating mu receptor desensitization. The biased agonist profile and partial mu receptor agonism likely underlie important safety advantages, including a ceiling effect for respiratory depression (8) and reduced misuse liability (9).

A systematic review and meta-analysis of randomized controlled trials comparing the effects of buprenorphine to those of an active control or placebo on chronic noncancer pain found that buprenorphine had a statistically significant advantage over placebos and active analgesics (10). Another similar systematic review and meta-analysis involving OUD and non-OUD populations also identified significantly reduced pain scores in the buprenorphine group, an effect that was larger in the non-OUD group (11).

Davis identifies advantages of buprenorphine compared with FAO for the treatment of chronic pain, including the former substance's effectiveness against multiple pain phenotypes, reduced analgesic tolerance, less constipation and cognitive dysfunction, safety in elderly patients and in those with liver and kidney disease, and milder withdrawal syndrome (12). Some of these purported advantages were borne out in clinical trials comparing buccal buprenorphine to long-acting common FAO, which found reduced nausea, vomiting, constipation, headache, dizziness, and somnolence in the groups of patients who used buprenorphine (13). Patients who transitioned from COT to buprenorphine have been shown to experience a reduction in the adverse psychological effects associated with COT (e.g., anxiety, depression) (14); kappa and delta receptor antagonism may contribute to these benefits.

There are a variety of published strategies to transition from FAO to buprenorphine for OUD and or pain, and these strategies have a generally high success rate, regardless of approach (15). Reviews assess-

ing transitions to buprenorphine typically emphasize baseline opioid and MME and acknowledge a general lack of data on the patient factors that may affect outcomes (16). In this study, we searched a large database to determine the factors associated with a successful transition to buprenorphine.

Methods

Study Design and Data Source

This retrospective cohort study utilized the Veterans Affairs (VA) Corporate Data Warehouse (CDW), a comprehensive repository of clinical and administrative data for veterans receiving care through the VA health care system. The period studied spanned from 2010 to 2022, and the researchers focused on patients who received outpatient opioid prescriptions. The VA Western New York Healthcare System Institutional Review Board approved this study, granting a waiver of informed consent under HIPAA regulations.

Data Extraction and Management

We queried the CDW using Microsoft SQL Management Studio Version 18.9.1 on the VA Informatics and Computing Infrastructure (VINCI) workspace. Subsequently, the extracted data were imported into RStudio and Python within the VINCI environment for cleaning, processing, and analysis.

Study Population

The study cohort comprised patients who received new prescriptions for microgram-strength buprenorphine formulations, including buccal and transdermal preparations, between 2017 and 2022 (n = 15,291). We excluded milligram-strength sublingual preparations typically used for OUD treatment. However, patients with a diagnosis of OUD were included in the study. The cohort included both patients previously on COT and those receiving BUP as a new opioid analgesic in an acute or subacute setting.

Opioid Prescription Analysis

We extracted all outpatient opioid prescriptions for each patient from one year before BUP initiation to one year after it. The maximum daily dose (MDD) was calculated using structured data elements from the prescription records, including strength, quantity, and duration. We created a day-by-day summary of MDD for each patient-opioid combination, allowing for the calculation of weekly and monthly average MDD. The total morphine milligram equivalent dose (MED) was determined by multiplying the MDD by the appropriate conversion factor from the published CDC conversion table (2). Due to buprenorphine's unique pharmacological properties and unclear equivalency to FAO, buprenorphine was not included in aggregate opioid dose calculations.

Patient Characteristics

Demographic variables, including age, gender, race, and ethnicity, were extracted from the CDW. We identified episodes of care associated with specific clinical services using VA stop codes, including Pain Clinic (code 420), Psychology (code 510), Physical Rehabilitation Medicine (code 201), Physical Therapy (code 205), and substance use disorder treatment (code 513).

Comorbidities were assessed using ICD-10 diagnosis codes collected for the 12 months before buprenorphine initiation and analyzed using the Elixhauser Comorbidity Index and scoring system (17). Emergency room encounters were identified using CPT codes and tabulated for the year before and after BUP introduction.

Outcome Measures

Primary Outcome

The primary outcome was a successful rotation to buprenorphine, defined as the continuation of microgram dosing of transdermal or buccal buprenorphine for at least 3 months with a refill rate ≥ 75%. The refill rate was calculated as the number of days buprenorphine was prescribed divided by the total number of days between the first and last prescription.

Secondary Outcomes

The secondary outcome measure was the prescription of FAO. Aggregate opioid prescription measures were calculated as described above before and after the introduction of buprenorphine.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and outcomes. Continuous variables were compared using 2-way t-tests, with logarithmic transformation applied to opioid MED data due to skew. Categorical variables were analyzed using chi-squared tests. The Bonferroni correction was applied for multiple comparisons.

A generalized additive model (GAM) was em-

ployed for sensitivity analysis and to investigate associations between independent variables and successful buprenorphine initiation. A Cox proportional hazard model was used to examine the effects of key variables identified in the GAM on buprenorphine discontinuation.

Exploratory analyses were performed to investigate possible phenotypic clustering of patients based on buprenorphine rotation outcomes. The effects of independent variables, including patient factors and pre-rotation opioid prescriptions, were examined by selectively excluding them from the analysis to determine their impact on outcome variables.

All statistical analyses were performed using RStudio, with a significance level set at $P < 0.05$.

Results

Most patients were 50 years of age or older (83.2%), with the largest proportion (34.0%) in the 65-74 age range. Men comprised 87.7% of the sample, and 76.9% of the patients identified as White. Among nonopioid medications, gabapentin was prescribed to 27.6% of the patients, pregabalin to 16.6%, and duloxetine to 20.3%. Tricyclic antidepressants were prescribed to 5.4% of the population. These characteristics of the study population are presented in Table 1.

Oxycodone was the most commonly prescribed opioid (n = 3,994), followed by hydrocodone (n = 3,517), tramadol (n = 1,822), and morphine (n = 1,295), while other opioids, such as fentanyl, methadone, and tapentadol were prescribed less frequently. Figure 1A illustrates the distribution of these pre-buprenorphine opioid prescriptions.

The buprenorphine continuation rates associated with the various pre-exposure opioids ranged from approximately 30% to 45%. While slight variations were observed among patients who used different pre-exposure opioids, with morphine and tapentadol showing the highest continuation rates and hydromorphone and codeine the lowest, the 95% confidence intervals for all pre-exposure opioids overlapped. This overlap indicates that there were no statistically significant differences in buprenorphine continuation rates based on pre-exposure opioid type. Figure 1B illustrates these buprenorphine continuation rates.

The mean morphine milligram equivalent (MME) exposure for patients who continued buprenorphine treatment was 33.1 ± 39.5 (mean ± SD), while for those who discontinued, the mean was 33.4 ± 43.5. A two-tailed t-test demonstrated no significant difference ($P = 0.71$) between the average MME of patients who continued buprenorphine and those who did not. Figure 2 compares mean pre-exposure MME rates between the two groups.

There was a reduction in both the total dose prescribed and the number of patients receiving prescriptions for various opioids before and after buprenorphine exposure. For all opioids listed, there was a decrease in the total dose prescribed to the study population after the patients were exposed to buprenorphine. The most substantial reductions in total dose were observed for fentanyl (362,000 mcg/hour, 74.5% decrease), morphine (3,026,000 mg, 70.9% decrease), and methadone (327,000 mg, 70.5% decrease). Other opioids also showed notable reductions in dosage: hydromorphone (46,000 mg, 36.2%), hydrocodone (2,788,000 mg, 55.1%), and oxycodone (3,031,000 mg, 46.9%). Tramadol, often considered a weaker opioid, showed a reduction of 8,465,000 mg (46.5%). The number of patients receiving prescriptions for each opioid also decreased post-buprenorphine exposure in the cases of most opioids, except for tapentadol, which saw a slight increase from 81 to 100 patients but was prescribed infrequently. Table 2 presents aggregate opioid prescriptions before and after buprenorphine exposure.

A GAM was employed to examine associations between patient factors and continued buprenorphine use. The results of this analysis are presented in Fig. 3. Notably, both COT groups (i.e., both the weaned and unweaned groups) showed an increased likelihood of continuing buprenorphine use compared to patients who had not received continuous opioids prior to exposure, with the pre-rotation weaning group demonstrating a higher odds ratio for continuation (OR: 1.45, 95% CI: 1.30-1.62) than the group that was not weaned (OR: 1.22, 95% CI: 1.09-1.36), although there was overlap in the 95% confidence interval ranges. Interestingly, there was no significant association observed between opioid strength or potency and the likelihood of buprenorphine continuation, as evidenced by the overlapping confidence intervals for different opioid types.

Odds ratios for various clinical factors associated with buprenorphine continuation are presented in Fig. 3. Healthcare utilization data showed that emergency room visits were associated with lower odds of continuation (OR: 0.76, 95% CI: 0.68-0.84), while pain clinic visits were associated with higher odds (OR: 1.22, 95% CI: 1.10-1.34). Psychotherapy and psychology visits

Table 1. *Demographics*.

Characteristic	Category	Count (%)
Age Group	18 to 34	414 (2.7%)
	35 to 49	2,093 (13.6%)
	50 to 64	5,083 (33.1%)
	65 to 74	5,224 (34.0%)
	75 and older	2,477 (16.1%)
Race	White	11,822 (76.9%)
	Black or African American	2,078 (13.5%)
	American Indian or Alaska Native	189 (1.2%)
	Asian	93 (0.6%)
	Native Hawaiian or Other Pacific Islander	139 (0.9%)
	Unknown	970 (6.3%)
Ethnicity	Not Hispanic or Latino	13,821 (89.9%)
	Hispanic or Latino	816 (5.3%)
	Unknown	654 (4.3%)
Gender	Male	13,479 (87.7%)
	Female	1,812 (11.8%)
Pregabalin	Prescribed	2,550 (16.6%)
Gabapentin	Prescribed	4,249 (27.6%)
TCA	Prescribed	830 (5.4%)
Duloxetine	Prescribed	3,125 (20.3%)

showed a positive association, but this finding was not statistically significant. The presence of illicit drug use (cocaine and heroin) was associated with lower odds of continuation (OR: 0.62, 95% CI: 0.39-0.99). No significant association was observed between cannabis use and continuation odds.

Figure 4 presents the dose-response curve from the GAM analysis, exploring the relationship between the prior MED and the odds ratio of buprenorphine continuation. The curve reveals a nonlinear relationship between MED and continuation odds. The dose-response curve remains relatively stable for MME between 0-50 mg. Beyond 50 MME, the odds of buprenorphine continuation decrease, with the decline becoming more pronounced as MED approaches 200 mg. The estimate is less certain for higher opioid doses, as evidenced by the widening 95% confidence interval. The smooth term for the MED spline curve is statistically significant ($P = 0.007$), suggesting exposure to higher opioid doses is associated with reduced odds of continuation of buprenorphine. However, the model explains a small proportion of the total variance (deviance explained = 1.08%, adjusted R-squared = 0.012).

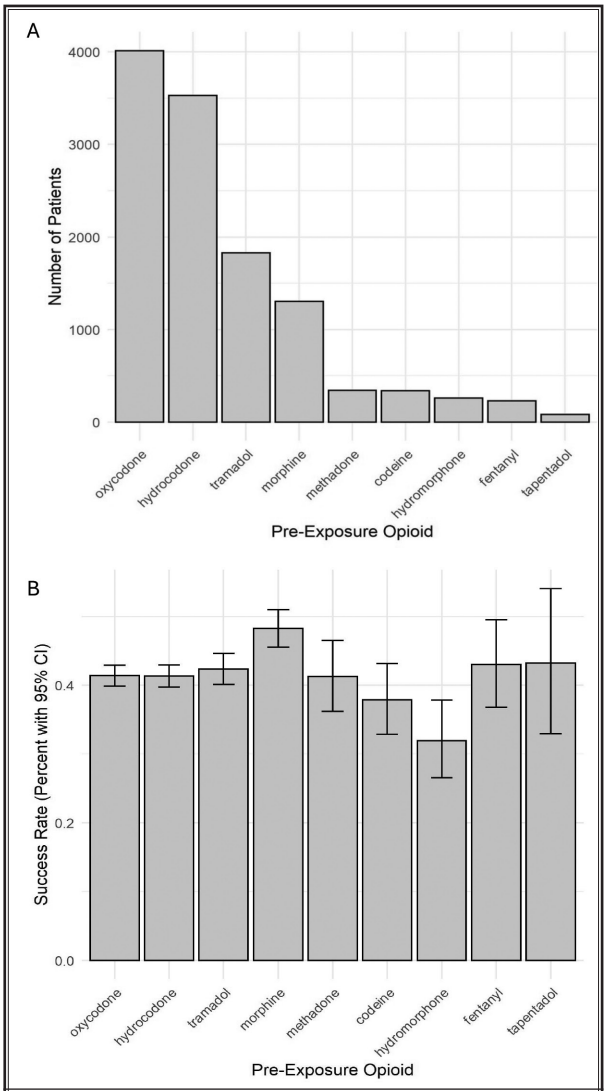

Fig. 1. *Pre-exposure opioid distribution and buprenorphine trial success rates.*
A) Number of patients prescribed various opioids before buprenorphine initiation. B) Success rates of buprenorphine trials for patients based on their pre-exposure opioid. Bars represent the percentage of successful trials, with error bars indicating 95% confidence intervals.

Discussion

Transitions from COT to buprenorphine are increasingly recommended for patients receiving daily full agonist opioids for chronic pain. Multiple successful strategies for implementing these shifts have been employed, but there is no widely accepted standard. Our findings within a large VA dataset provide insight into

analgesic prescribing practices within VA and identify factors that may impact transition success.

Our data set reflects the population of veterans who receive care in the VA system. For comparison, 2017 census data showed that the VA population is 93.3% men and 46.3% age 65 or greater. The 2017 census also demonstrated that veterans in general were 82.2% White (18). These data are similar to those in our sample (87.7% men, 50.1% 65 and greater, and 76.9% White).

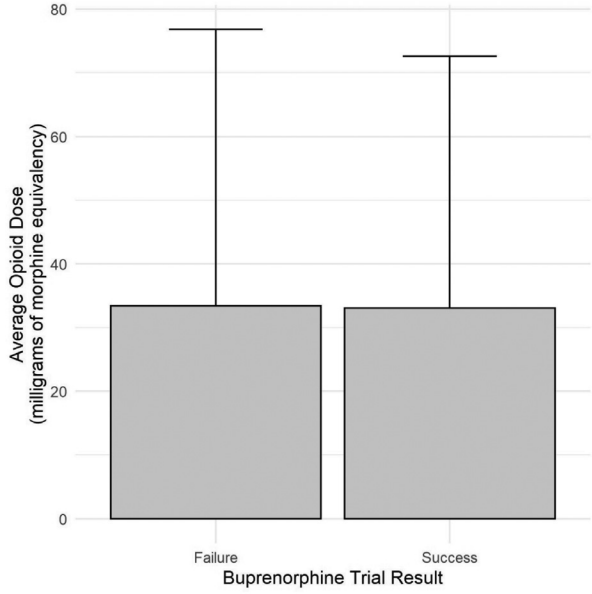

Fig. 2. *Average pre-exposure opioid dose in morphine milligram equivalents (MME) for successful and failed buprenorphine trials (mean and SD; P-value = 0.71).*

Gabapentinoids, particularly gabapentin, and the SNRI duloxetine were often prescribed. Oxycodone and hydrocodone were the most commonly prescribed opioids, followed by tramadol and morphine, with other opioids prescribed much less frequently. Interestingly, across the range of these various opioids, including opioids of various potencies, there was no association between pre-exposure opioids and continued buprenorphine use in the study population.

While the mean MME was similar between successful and failed buprenorphine trials in the aggregate data, the regression model suggested that increasing MME was associated with reduced odds of successful buprenorphine continuation, particularly when the MME was above 90. Importantly, buprenorphine exposure was associated with reductions in prescribed opioid MME, regardless of whether the buprenorphine use was continued, plausibly mitigating the established harms of COT. Larger reductions in the prescription of FAO were most pronounced in the group that continued buprenorphine, indicating that buprenorphine could replace conventional opioids for some patients undergoing COT. The long-term success of buprenorphine initiation may relate to the process of preparing patients and supporting them throughout the buprenorphine trial. Similarly, pain clinic visits predicted successful continuation, whereas emergency room visits and illicit drug use were associated with lower odds of success.

Limitations

This study's limitations are typical of large-scale observational studies, including imperfect data quality/

Table 2. *Aggregate opioid prescriptions before and after buprenorphine exposure. Doses are presented in thousands of milligrams. Patient counts represent the number of individuals prescribed each opioid. Pre-exposure data reflect opioid prescriptions before buprenorphine initiation, while post-exposure data show prescriptions following buprenorphine treatment, regardless of whether the buprenorphine prescriptions were continued.*

Drug	Pre-Exposure Dose (1000 mg)	Post-Exposure Dose (1000 mg)	Pre-Exposure Patients	Post-Exposure Patients
Codeine	1,707	1,085	336	236
Fentanyl	486	124	229	95
Hydrocodone	5,058	2,270	3,517	2,072
Hydromorphone	127	81	260	206
Methadone	463	136	342	162
Morphine	4,266	1,240	1,295	583
Oxycodone	6,464	3,433	3,994	2,710
Tapentadol	772	743	81	100
Tramadol	18,205	9,740	1,822	1,030

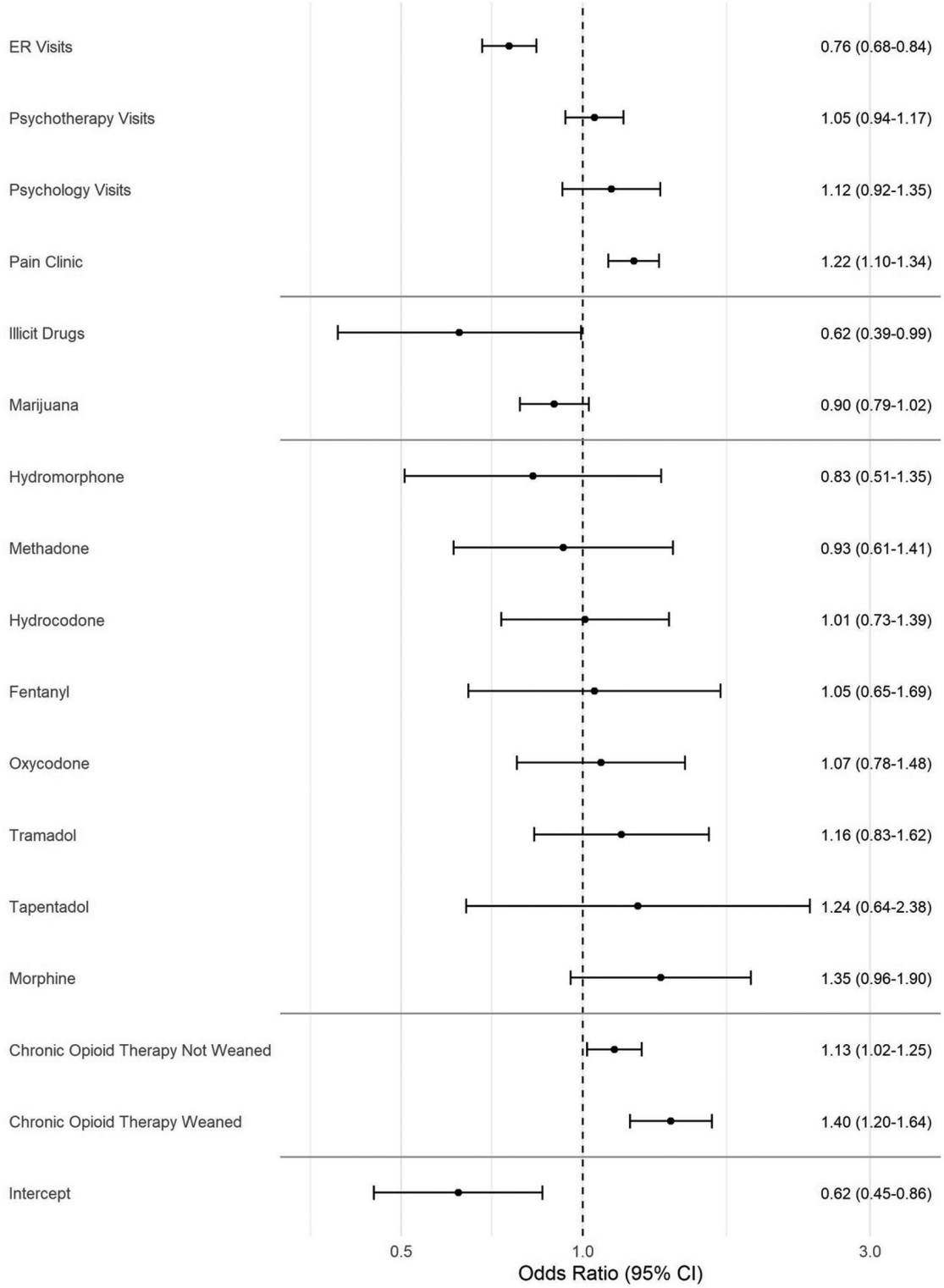

Fig. 3. *Forest plot of odds ratios for factors associated with successful buprenorphine continuation. Points represent odds ratios, and horizontal lines indicate 95% confidence intervals. The vertical dashed line at 1.0 represents no effect. Odds ratios to the right of this line indicate increased odds of success, while those to the left indicate decreased odds.*

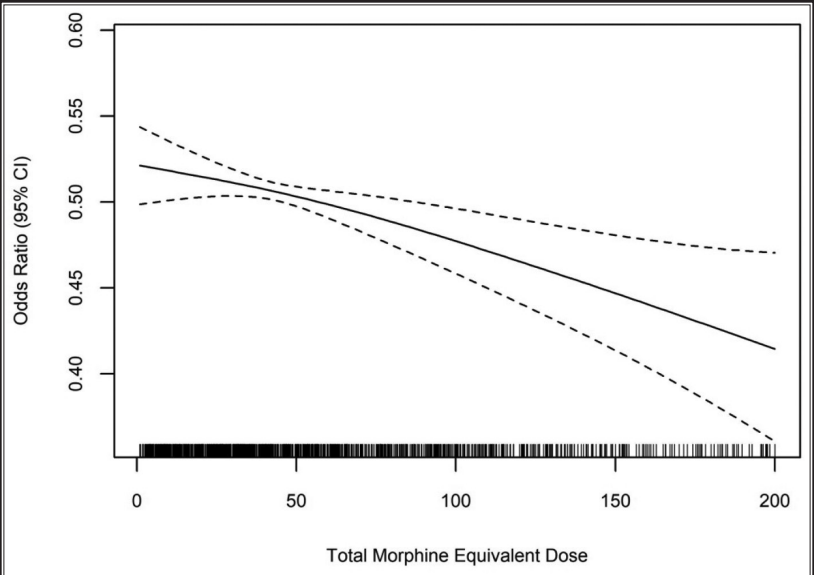

Fig. 4. *Generalized additive model (GAM) spline curve showing the relationship between total morphine equivalent dose (MED) and the odds ratio of successful buprenorphine continuation. The solid line represents the estimated effect, and the dashed lines represent the 95% confidence interval.*

integrity, incomplete data, and the use of stop codes and CPT codes to determine the nature of a clinical encounter. The dataset is limited to the information collected, which excludes other factors likely associated with the outcome. Our findings also depend on the accuracy of the CDW data, which can be affected by erroneous data in the prescription or clinic encounter data tables. Data from prescription records may not reflect patient intake accurately, and patients may have used medications from non-VA or nonmedical sources. We used the continuous prescription of buprenorphine as a surrogate marker of successful transition. The population of the Veterans Health Administration is not representative of other populations, and the results may not generalize to other patient populations in the United States or other countries.

Conclusion

Our analysis of a large VA dataset provides some insight into the use of buprenorphine in a large nationwide health care system, including the substance's utility in rotation from COT, which is an increasingly common clinical scenario. We identified significant reductions in the number of patients prescribed FAO and the total dose of opioids prescribed to this population of patients exposed to buprenorphine, with the largest effect observed in patients who continued using buprenorphine after exposure. This study was not designed to determine if buprenorphine exposure was causally related to reduced opioid use, so the effect may be due to general efforts to wean patients from opioids. While the potency and dose of baseline COT were not predictive of buprenorphine continuation, the multivariable analysis suggested that higher opioid doses (> 90 MME) were associated with a decreased likelihood of continuation. Factors correlating with patient support throughout the process, such as weaning from COT and pain clinic visits, were associated with buprenorphine continuation. In contrast, emergency room visits, which suggested reduced support throughout the process, were associated with lower odds of continuation. Finally, cocaine and heroin use were similarly associated with lower odds of continuation. These findings support the recommendation to trial buprenorphine in patients undergoing COT and suggest that patient factors and shared decision-making are more important predictors of success than the pharmacological properties, potency, or dose of pre-rotation opioid exposure.

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