# Buprenorphine Dosage and Urine Quantitative Buprenorphine, Norbuprenorphine, and Creatinine Levels in an Office-Based Opioid Treatment Program

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## ABSTRACT

**BACKGROUND:** Treatment progress is routinely monitored by urine testing in patients with opioid use disorder (OUD) undergoing buprenorphine medication-assisted treatment (MAT). However, interpretation of urine test results could be challenging. This retrospective study aims to examine the results of quantitative buprenorphine, norbuprenorphine, and creatinine levels in urine testing in relation to sublingual buprenorphine dosage to facilitate an accurate interpretation of urine testing results.

**METHODS:** We reviewed the medical charts of 41 consecutive patients, who were residing in halfway houses where their medication intake was closely monitored and who had enrolled in an office-based MAT program at an urban clinic between July 2018 and June 2019. The patients' urine testing results were reviewed, and demographic variables were recorded. We focused on the patients treated with 8-, 12-, or 16-mg/day of buprenorphine, examining their urine buprenorphine, norbuprenorphine, and creatinine levels. Analysis of variance tested the statistical association between the dosage and urine testing results on the norbuprenorphine-to-creatinine ratio.

**RESULTS:** A total of 240 urine samples from 41 patients were included for this study. The 41 patients received a mean buprenorphine dose of 10.5 ± 3.7 mg/day (range, 4-20 mg/day). Then, this study examined the distribution of the 240 urine samples and then focused on 184 urine samples that came from the 33 patients who were treated with 8-, 12-, and 16-mg/day of buprenorphine, the 3 most common dosages. All of the 184 urine samples had a creatinine level of >20 mg/dL and buprenorphine-to-norbuprenorphine ratio <50:1. The average norbuprenorphine-to-creatinine ratio in the 8 mg/day dosage group was $3.85 \pm 2.24 \times 10^{-4}$ (n = 66; range, 0.44-11.12). The respective ratios in the 12- and 16-mg dosage groups were $5.64 \pm 3.40 \times 10^{-4}$ (n = 83; range, 1.55-22.72) and $6.23 \pm 4.92 \times 10^{-4}$ (n = 35; range, 1.37-27.12). The 3 dosage groups differed significantly in the mean ratios ($P < .01$), except when the 12- and 16-mg dosage groups were compared ($P = .58$). The results of this study thus suggest that prescribers should pay attention to the following features: (1) unexpected substance(s) in urine testing, (2) creatinine level under 20 mg/dL, (3) buprenorphine-to-creatinine ratio over 50:1, (4) buprenorphine dosage over 24 mg/day, and (5) norbuprenorphine-to-creatinine ratio consistently under $0.5 \times 10^{-4}$ in patients treated with 8 mg/day or $1.5 \times 10^{-4}$ in patients treated with 12 mg/day or more.

**CONCLUSION:** This study suggested parameters for interpreting quantitative urine test results in relation to buprenorphine intake dose in office-based opioid treatment programs.

**KEYWORDS:** Buprenorphine, norbuprenorphine, creatinine, opioid use disorder, medication-assisted treatment, urine testing

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## Introduction

Opioids are substances that attach to opioid receptors, especially the *mu* subtype.[1] Because of their addictive nature, numerous opioid-related deaths have been reported, and the number has been drastically increasing.[2] One cause for the increase in the death rate is related to opioid use disorder (OUD), which contributes to the increased use of illegal heroin and fentanyl.[3] Buprenorphine, a partial agonist with a "ceiling effect," is one of the FDA-approved drugs for medication-assisted treatment (MAT) of OUD.[4]

Buprenorphine metabolism is complicated with various metabolites involved in the pathway, but it is primarily metabolized by P450 3A4.[5] Buprenorphine is metabolized to buprenorphine-3-glucuronide (Bup-G) and norbuprenorphine, which is further metabolized to norbuprenorphine-3-glucuronide (Norbup-G).[6] Confirmatory laboratory results reveal quantitative buprenorphine, norbuprenorphine, and creatinine levels. The quantitative results for buprenorphine include buprenorphine and Bup-G, whereas those for norbuprenorphine include norbuprenorphine and Norbup-G. Although compliant patients in buprenorphine treatment programs have lower levels of buprenorphine and higher levels of norbuprenorphine, intermittent buprenorphine use results in much lower metabolite levels.[7]

Buprenorphine level in the urine starts increasing after buprenorphine intake, while the norbuprenorphine level, which lags behind it, surpasses the buprenorphine level approximately 7 hours after a single dose buprenorphine intake. Namely, Kronstrand et al.[8] studied 18 healthy volunteers who took a single 0.4 mg dose of buprenorphine. The researchers followed the buprenorphine and norbuprenorphine levels in their urine and found high buprenorphine levels and low norbuprenorphine levels immediately after intake. However, the norbuprenorphine level surpassed the buprenorphine level approximately 7 hours after the buprenorphine intake. Therefore, the timing of buprenorphine intake could influence the quantitative results of buprenorphine and norbuprenorphine levels, especially following a single dose intake.

Diversion of buprenorphine products has become a serious problem in office-based MAT programs in the US.[9] Patients reportedly perform various manipulations to mask inappropriate urine test results and hide their non-compliance with buprenorphine treatment. One such manipulation is known as "adulteration." Urine samples could be tainted with various substances such as nitrite and glutaraldehyde to manipulate their drug testing results.[10] Another manipulation strategy is to directly dip the buprenorphine in the urine sample, known as "spiking." Many studies aimed to detect spiking. Accurso et al.[11] found that the buprenorphine-to-norbuprenorphine ratio in buprenorphine spiked samples was greater than 50:1. Donroe et al.[12] argued that buprenorphine levels equal to or above 700 ng/mL could indicate adulteration. Suzuki et al.[7] reported that all samples suspected of buprenorphine spiking had a buprenorphine level higher than 2000 ng/mL and a mean norbuprenorphine level of 11.9 ng/mL. These studies indicated that inappropriate proportions of buprenorphine and norbuprenorphine in the urine samples could reveal urine sample manipulations.

Dilution is another method used to prevent the detection of inappropriate substances in urine samples. Adding water to urine samples could dilute them enough to make the levels of such substances lower than the minimum detection level. Dilution manipulations could be detected by measuring the creatinine level, which should be above 20 mg/dL.[10] Measuring the urine creatinine is important when monitoring the levels of buprenorphine and norbuprenorphine because urine concentration could fluctuate, depending on the hydration status of the patient. Weigand[13] suggested that urine creatinine could be used to standardize the norbuprenorphine level because it indicates how concentrated the urine is. Therefore, buprenorphine, norbuprenorphine, and creatinine levels should be monitored in patients under buprenorphine MAT to identify any urine manipulation and monitor treatment progress.

This retrospective study aimed to examine the quantitative buprenorphine, norbuprenorphine, and creatinine urine testing results in patients on buprenorphine in an office-based MAT and residing in halfway houses where their buprenorphine administration was closely monitored. We hypothesized that there is an association between these levels and buprenorphine dosage. The results of this study could facilitate an accurate interpretation of urine testing and consequently, help improve buprenorphine treatment for optimal patient care.

## Methods

### *Setting*

This retrospective study was conducted at an urban MAT clinic in NY State after obtaining the Institutional Review Board (IRB) approval (IRB Protocol ID: 20-HELI-101). The need to obtain informed consent was waived due to the retrospective nature of the study.

### *Chart review*

The following information was extracted from the electronic health record: demographic information that included the number of days in the halfway house program, sex, age, body mass index (BMI), employment status, race/ethnicity, marital status, education, smoking, veteran status, and buprenorphine dosage. The maximal buprenorphine dose was recorded for analysis of patients' dosage distribution if any dosage adjustment occurred during the study period. We also retrieved the quantitative urine results of buprenorphine, norbuprenorphine, and creatinine. The participants' buprenorphine prescription was verified with the NY State Prescription Drug Monitoring Program (PDMP).

### *Participants*

We reviewed the medical records of 281 patients living in halfway houses and treated at an office-based buprenorphine MAT clinic following a diagnosis of OUD between July 1, 2018 and June 30, 2019. The halfway house staff closely monitored the patients' medication intake; therefore, the residents were less likely to be non-compliant with the buprenorphine treatment than those in a regular office-based MAT program. The inclusion criteria were: (1) resident in a halfway house for >6 days; (2) with a history of OUD; (3) was on buprenorphine during the study period, which was verified with the PMDP; and (4) available quantitative urine testing for buprenorphine, norbuprenorphine, and creatinine levels.

Of the 281 halfway house residents, 166 had a diagnosis of OUD reported in their electronic medical records, while the others had other substance use disorders such as alcohol and stimulants. Of these 166 patients, 89 were on buprenorphine products during the study period, and their prescriptions were verified with the NY State PDMP. Of these 89 patients, we analyzed the data of 41 (15.59% of the 281 halfway house residents), for whom quantitative measurements of urine buprenorphine, norbuprenorphine, and creatinine were available. A flowchart displaying the patient selection process is presented in Figure 1.

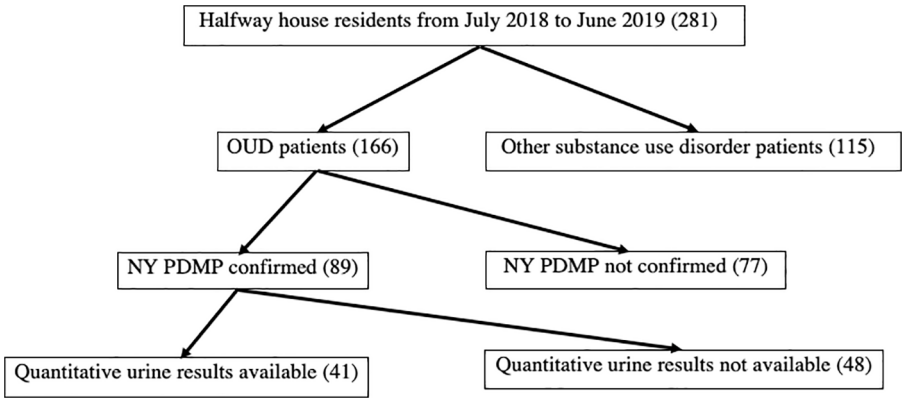


**Figure 1.** Patient selection process. The number in each box indicates the number of patients in each category.
Abbreviations: OUD, opioid use disorder; PDMP, prescription drug monitoring program.

### *Urine samples*

Quantitative measurements of urine buprenorphine, norbuprenorphine, and creatinine were available for 245 samples from the 41 patients. However, we applied the following exclusion criteria to select urine samples: (1) urine samples during the first 6 day stay at the halfway houses, (2) urine samples contained other substance(s), and (3) urine creatinine <20 mg/dL. We excluded 4 urine samples obtained while the patients had stayed in the halfway houses for fewer than 6 days as such samples could not reflect their monitored buprenorphine intake. We also excluded urine samples positive for any substance other than buprenorphine. One urine sample was excluded as it was positive for tetrahydrocannabinol (THC), a potential P450 3A4 inhibitor that might interact with buprenorphine metabolism.[14] Another exclusion criterion was creatinine level <20 mg/dL[10]; however, creatinine level in all urine samples was >20 mg/dL. As a result, 240 urine samples from 41 patients were included in this study.

### *Data analysis*

Descriptive statistics were used to analyze the results and examine the dosage distribution of the 41 patients. The demographic information of the 41 patients was reviewed, and their dosages and distribution among the 240 urine samples were determined. We decided to focus on the urine samples from the patients treated with 8-, 12-, or 16-mg/day buprenorphine, the 3 most common dosages, 184 urine samples in total. We analyzed the urine samples, exploring buprenorphine, norbuprenorphine, and creatinine levels as well as the ratios of buprenorphine-to-norbuprenorphine, buprenorphine-to-creatinine, and norbuprenorphine-to-creatinine separately within each dosage group. Analysis of variance (ANOVA) compared the mean ratios of buprenorphine-to-norbuprenorphine, buprenorphine-to-creatinine, and norbuprenorphine-to-creatinine among the 3 dosage groups, setting the significance level at ($\alpha = .05$). The correlation coefficients ($r$) between buprenorphine and norbuprenorphine, buprenorphine and creatinine, and norbuprenorphine and creatinine were analyzed within each dosage group. Continuous variables are presented as mean ± standard deviation. These statistical analyses were performed using Microsoft Excel.

The urine tests were conducted by Quest Diagnostics, where buprenorphine and norbuprenorphine test results were expressed in ng/mL and creatinine in mg/dL. The ratios of buprenorphine-to-creatinine and norbuprenorphine-to-creatinine were therefore expressed as ($\times 10^{-4}$) for an easier understanding. The maximum measurable levels of buprenorphine and norbuprenorphine were 2000 ng/mL, so concentrations higher than this level were noted as >2000 ng/mL in the test reports and counted as 2000 ng/mL for this study analysis. This adjustment could cause some inaccuracy in the analysis results. There was 1 case of >2000 ng/mL norbuprenorphine in the 8 mg/day dosage group, 1 case of >2000 ng/mL buprenorphine and 8 cases of >2000 ng/mL norbuprenorphine in the 12 mg/day dosage group, and 2 cases of >2000 ng/mL norbuprenorphine in the 16 mg/day dosage group.

## Results

### *Demographic information*

Demographic characteristics of the 41 patients residing in halfway houses that met the inclusion criteria are shown in Table 1.

### *Dosage*

All patients were treated with sublingual buprenorphine/naloxone products (Suboxone), but this study focused on buprenorphine dosage only because naloxone exerts no significant clinical effect when taken sublingually as prescribed.[15]

The study included 41 patients (male, 36; female, 5) who received the following doses: 4 mg/day (n = 2), 6 mg/day (n = 2), 8 mg/day (n = 17), 10 mg/day (n = 1), 12 mg/day (n = 10), 14 mg/day (n = 2), 16 mg/day (n = 6), or 20 mg/day (n = 1). The mean dosage was 10.5 ± 3.7 mg/day (mode, 8 mg/day; median, 11 mg/day; Figure 2).

**Table 1.** Demographic information.

| CHARACTERISTIC (N = 41) | MEAN ± SD OR N (%) | RANGE |
|---|---|---|
| Age (y) | 34.8 ± 8.8 | 25-63 |
| Sex, male | 36 (87.8) | |
| Ethnicity | | |
| White | 36 (87.8) | |
| Black | 3 (7.1) | |
| Hispanic | 1 (2.4) | |
| Other | 1 (2.4) | |
| Marital status | | |
| Single | 38 (92.7) | |
| Divorced | 2 (4.9) | |
| Separated | 2 (4.9) | |
| Married | 1 (2.4) | |
| Employment | | |
| Unemployed | 41 (100) | |
| Days in halfway house | 13.2 ± 98.7 | 12-351 |
| BMI (kg/m$^2$) | 26.8 ± 3.7 | 21-40 |
| Smoking | | |
| Smoker | 38 (92.7) | |
| Former smoker | 2 (4.9) | |
| Never | 1 (2.4) | |
| Veterans | 1 (2.4) | |
| Education | | |
| <High school | 7 (17.1) | |
| High school | 12 (29.3) | |
| Some college | 11 (34.4) | |
| Bachelor's | 2 (4.9) | |

Abbreviation: BMI, body mass index.
The data sets are presented as mean ± standard deviation or n (%).

A total of 240 urine samples were analyzed, which is illustrated in Figure 3 below. Most of the samples were from patients receiving 8 mg/day (n = 66 from 20 patients), 12 mg/day (n = 83 from 16 patients), and 16 mg/day (n = 35 from 10 patients). Many patients' dosages were adjusted during the study period, so that more than 1 samples came from the same patient.

### *Urine analysis results for the 8-, 12-, and 16-mg/day dosage groups*

No suspected manipulation such as dilution was identified in the 184 urine samples. All had the creatinine level above 20 mg/dL[16]; the lowest creatinine level was 25 mg/dL in the 8 mg/day dosage group. The buprenorphine-to-norbuprenorphine ratios ranged between 0.04 and 5.82, considerably lower than the reported spiked ratio of >50:1.[11] Although some urine samples had high buprenorphine levels (>700 ng/mL), their corresponding norbuprenorphine levels were also much higher than the reported average level of suspected spiked samples (ie, 11.75 ng/mL).[7,12] These results indicated that it was unlikely that any of the urine samples was manipulated by dilution or spiking.

There were 66 urine samples in the 8 mg/day dosage group. The urine tests found a mean buprenorphine of 260 ± 304 ng/mL (range, 8-1530 ng/mL), norbuprenorphine of 596 ± 468 ng/mL (range, 45->2000 ng/mL), and creatinine of 149 ± 75 mg/dL (range, 25-428 mg/dL). The mean ratios were: buprenorphine-to-norbuprenorphine, 0.51 ± 0.75 (range, 0.04-5.82; $r = .51$); buprenorphine-to-creatinine, $1.58 \pm 1.39 \times 10^{-4}$ (range, $0.05\text{-}8.43 \times 10^{-4}$, $r = .57$); norbuprenorphine-to-creatinine, $3.85 \pm 2.24 \times 10^{-4}$ (range, $0.45\text{-}11.12 \times 10^{-4}$; $r = .64$).

There were 83 urine samples in the 12 mg/day dosage group. The urine tests found a mean buprenorphine of 388 ± 380 ng/mL (range, 24->2000 ng/mL), norbuprenorphine of 780 ± 583 ng/mL (range, 81->2000 ng/mL), and creatinine of 138 ± 72 mg/dL (range, 30-510 mg/dL). The mean ratios were: buprenorphine-to-norbuprenorphine, 0.56 ± 0.48 (range, 0.05-2.56; $r = .58$); buprenorphine-to-creatinine, $2.86 \pm 2.45 \times 10^{-4}$ (range, $0.14\text{-}14.90 \times 10^{-4}$; $r = .54$); norbuprenorphine-to-creatinine, $5.64 \pm 3.40 \times 10^{-4}$ (range, $1.55\text{-}22.72 \times 10^{-4}$; $r = .66$).

There were 35 urine samples in the 16 mg/day dosage group. The urine tests found a mean buprenorphine of 334 ± 259 ng/mL (range, 63-1220 ng/mL), norbuprenorphine of 870 ± 560 ng/mL (range, 164->2000 ng/mL), and creatinine of 155 ± 90 mg/dL (range, 49-473 mg/dL). The mean ratios were: buprenorphine-to-norbuprenorphine, 0.44 ± 0.25 (range, 0.11-1.33; $r = .72$); buprenorphine-to-creatinine, $2.24 \pm 1.35 \times 10^{-4}$ (range, $0.47\text{-}7.85 \times 10^{-4}$; $r = .72$); norbuprenorphine-to-creatinine, $6.23 \pm 4.92 \times 10^{-4}$ (range, $1.37\text{-}27.12 \times 10^{-4}$; $r = .53$).

The correlation coefficients ($r$) mentioned above ranged between .51 and .72, indicating moderate correlations between buprenorphine and norbuprenorphine, buprenorphine and creatinine, and norbuprenorphine and creatinine in these groups. These urine test results are summarized in Table 2.

This study focused on the urine norbuprenorphine-to-creatinine ratio because buprenorphine level can be high for at least 7 hours after buprenorphine intake,[8] while its metabolites, including norbuprenorphine, would be detected in urine samples for 3 to 4 days,[17] and because creatinine standardizes norbuprenorphine levels.[13] The distribution of norbuprenorphine-to-creatinine ratios in the 3 dosage groups is illustrated in Figure 4.

The figure shows that the 12 mg/day group had the widest interquartile range, with the largest number of urine samples (n = 83). The lowest norbuprenorphine-to-creatinine ratio in the 8 mg/day dosage group was $0.45 \times 10^{-4}$, while that was

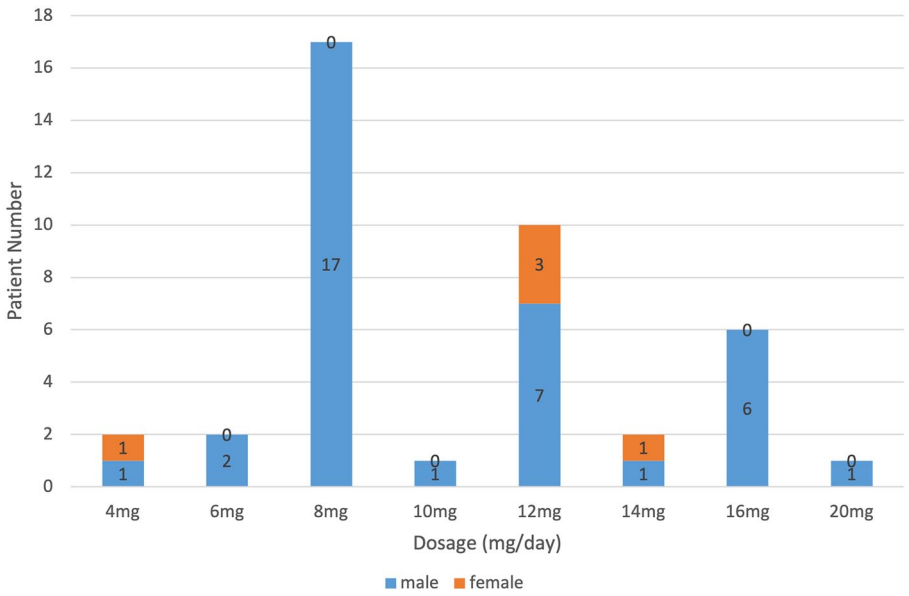


**Figure 2.** Patient number in each dosage group. The horizontal axis shows the buprenorphine dosage per day, while the vertical axis indicates the number of patients receiving each dosage per day. The numbers of patients are marked on the bars. The 3 most common dosages were 8-, 12-, and 16-mg/day. The blue bars indicate male while orange bars indicate female patients.

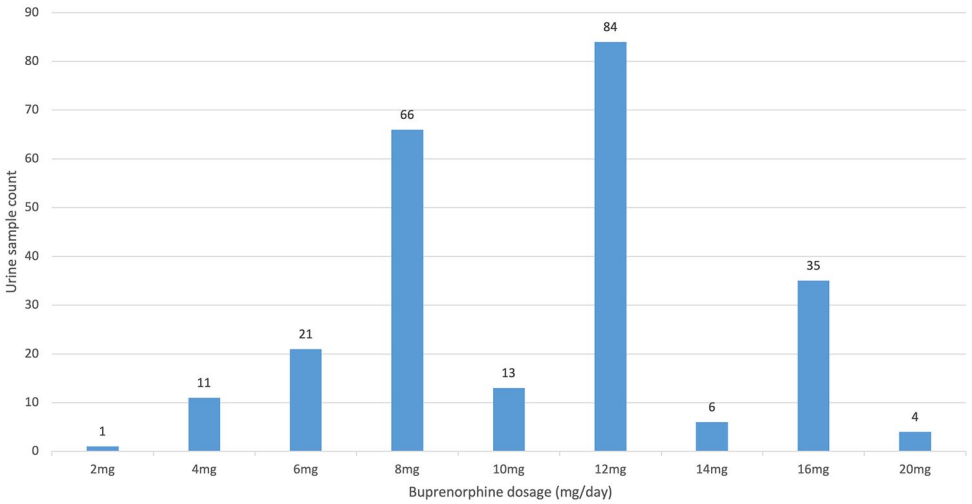


**Figure 3.** Dosage distribution and the urine samples. The horizontal axis shows the dosages that the patients were on, while the vertical axis indicates the number of urine samples obtained from these patients. The numbers of urine samples are marked on the bars. One urine sample came from a patient, who was on 2 mg/day, so the urine sample is listed as 2 mg/day in Figure 3, but his dosage was increased to 4 mg/day during the study period, so his dosage was counted as 4 mg/day in Figure 2.

$1.55 \times 10^{-4}$ and $1.37 \times 10^{-4}$ in the 12- and 16-mg/day dosage groups, respectively.

A one-way ANOVA compared the buprenorphine-to-norbuprenorphine ratios between the 3 groups and found them similar ($F[2, 178] = 0.51$, $P = .60$). The groups differed significantly in the buprenorphine-to-creatinine ratio ($F[2, 178] = 7.68$, $P < .01$). A Bonferroni post-hoc analysis indicated that the ratio in the 8 mg/day dosage group ($1.58 \pm 1.39 \times 10^{-4}$) was significantly lower than those in the 12- and 16-mg/day dosage groups ($2.86 \pm 2.44 \times 10^{-4}$ and $2.24 \pm 1.33 \times 10^{-4}$ respectively; $P < .01$ for both). However, the ratios in the 12- and 16-mg/day dosage groups were similar ($P = .15$).

A one-way ANOVA with the log-transformed data on the buprenorphine-to-creatinine ratios had a similar result ($F[2, 178] = 9.44$, $P < .01$) with a Bonferroni post hoc analysis indicating that the ratio in the 8 mg/day dosage group ($0.04 \pm 0.42 \times 10^{-4}$) was significantly lower than those in the 12- and 16-mg/day dosage groups ($0.31 \pm 0.39 \times 10^{-4}$ and $0.29 \pm 0.24 \times 10^{-4}$, respectively; $P < .01$ for both) However, the ratios in the 12- and 16-mg/day dosage groups were similar ($P = .71$).

We also compared the 3 groups for the norbuprenorphine-to-creatinine ratio and found them significantly different ($F[2, 178] = 6.81$, $P < .01$). A Bonferroni post-hoc analysis indicated that the ratio in the 8 mg/day dosage group ($3.84 \pm 2.24 \times 10^{-4}$)

**Table 2.** Summary of urine analysis in the 3 largest dosage groups.

| GROUP | 8 MG/DAY (N = 66) | 12 MG/DAY (N = 83) | 16 MG/DAY (N = 35) |
|---|---|---|---|
| Buprenorphine (ng/mL) | | | |
| Range | 8-1530 | 24->2000 | 63-1220 |
| Mean ± SD | 260 ± 304 | 388 ± 380 | 334 ± 259 |
| Norbuprenorphine (ng/mL) | | | |
| Range | 45->2000 | 81->2000 | 164->2000 |
| Mean ± SD | 596 ± 468 | 780 ± 583 | 870 ± 560 |
| Creatinine (mg/dL) | | | |
| Range | 25-428 | 30-510 | 49-473 |
| Mean ± SD | 149 ± 75 | 138 ± 72 | 155 ± 90 |
| Buprenorphine-to-norbuprenorphine ratio | | | |
| Range | 0.04-5.82 | 0.05-2.56 | 0.11-1.33 |
| Mean ± SD | 0.51 ± 0.75 | 0.56 ± 0.48 | 0.44 ± 0.25 |
| Correlation coefficient (*r*) | .51 | .58 | .72 |
| Buprenorphine-to-creatinine ratio ($\times 10^{-4}$) | | | |
| Range | 0.05-8.43 | 0.14-14.90 | 0.47-7.85 |
| Mean ± SD | 1.58 ± 1.39 | 2.86 ± 2.45 | 2.24 ± 1.35 |
| Correlation coefficient (*r*) | .57 | .54 | .72 |
| Norbuprenorphine-to-creatinine ratio ($\times 10^{-4}$) | | | |
| Range | 0.45-11.12 | 1.55-22.72 | 1.37-27.12 |
| Mean ± SD | 3.85 ± 2.24 | 5.64 ± 3.40 | 6.23 ± 4.92 |
| Correlation coefficient (*r*) | .64 | .66 | .53 |

Abbreviation: SD, standard deviation.

was significantly lower than those in the 12- and 16-mg/day dosage groups ($5.64 \pm 3.40 \times 10^{-4}$ and $6.23 \pm 4.92 \times 10^{-4}$, respectively; $P < .01$ for both). However, the ratios in the 12- and 16-mg/day dosage groups were similar ($P = .58$).

The log-transformed data on norbuprenorphine-to-creatinine ratios analyzed with a one-way ANOVA had also a similar result ($F[2, 178] = 9.66$, $P < .01$). A Bonferroni post hoc analysis showed that the ratio in the 8 mg/day dosage group ($0.50 \pm 0.29 \times 10^{-4}$) was significantly lower than those in the 12- and 16-mg/day dosage groups ($0.66 \pm 0.26 \times 10^{-4}$ and $0.72 \pm 0.24 \times 10^{-4}$, respectively; $P < .01$ for both). However, the 12- and 16-mg/day dosage groups had similar the ratios ($P = 0.64$), indicating that there was no significant difference between the 2 groups.

## Discussion

The urine samples on which this study focused had no sign of urine manipulation, as indicated by a creatinine level of >20 mg/dL and a buprenorphine-to-norbuprenorphine ratio of <50:1 in all.[11] This study also determined that the patients in halfway houses included in this study were treated with 4 to 20 mg/day of buprenorphine (mean, 10.5 mg/day), mostly ⩽16 mg/day. These results were consistent with previous studies on buprenorphine dosage in MAT programs. Zubieta et al.[18] reported that brain positron emission tomography (PET) scans showed that 2 mg of buprenorphine covered 36% to 50% of the *mu*-opioid receptors, while 16 mg covered 79% to 95% of them 4 hours after buprenorphine intake, indicating that 16 mg/day of buprenorphine was sufficient for most patients because its half-life is 28 to 37 hours.[19] Furthermore, Greenwald et al[20] argued that divided doses of 16 mg/day or lower would block the *mu*-opioid receptors in most individuals. These studies and the results of this study agree with Substance Abuse and Mental Health Services Administration's (SAMHSA's) recommendation to target treatment to 16 mg/day (range,

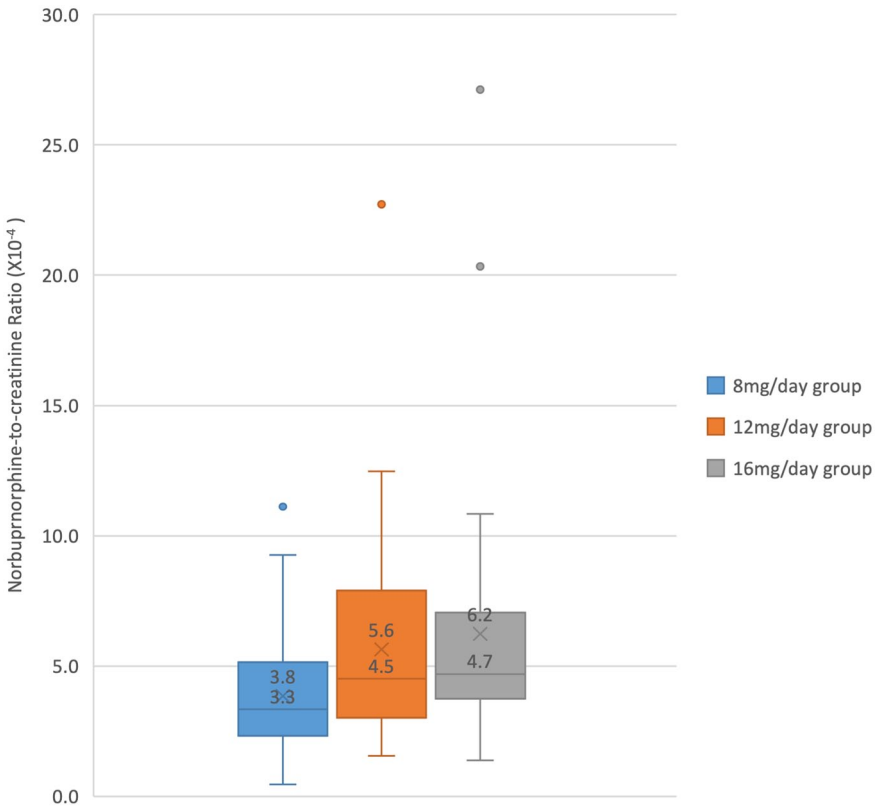


**Figure 4.** Norbuprenorphine-to-creatinine ratio distribution in the 3 dosage groups. The boxes represent the interquartile ranges and medians. The mean (×) and median values are indicated on the chart.

4-24 mg/day) of buprenorphine.[17] Thus, prescribers should be alarmed when prescribing buprenorphine at over 24 mg/day.

This study also showed that the 8 mg/day group presented a lower norbuprenorphine-to-creatinine ratio than the 12- and 16-mg/day groups, which were similar. This result might be associated with the "ceiling effect" of buprenorphine. In addition, the lowest norbuprenorphine-to-creatinine ratio in the 8 mg/day dosage group was $0.45 \times 10^{-4}$, while that was $1.55 \times 10^{-4}$ and $1.37 \times 10^{-4}$ in the 12- and 16-mg/day dosage groups, respectively. If the ratios in urine samples from a patient are consistently lower than these values, buprenorphine prescribers should pay close attention to the test results and attentively monitor the patient's treatment progress.

This study's results could be applied to the clinical decision-making process in office-based buprenorphine MAT programs by drawing attention to any of the following urine test results: (1) unexpected substance(s) found in the urine sample; (2) creatinine level under 20 mg/dL; (3) buprenorphine-to-norbuprenorphine ratio over 50:1; (4) buprenorphine dosage over 24 mg/day; and (5) norbuprenorphine-to-creatinine ratio consistently under $0.5 \times 10^{-4}$ in patients treated with 8 mg/day or $1.5 \times 10^{-4}$ in patients treated with 12 mg/day or more.

These features should prompt buprenorphine prescribers to pay close attention to the current treatment and if necessary, adjust it for optimal treatment outcomes rather than reprimanding their patients. For example, if the urine testing has at least one of the above features, prescribers could suspect that the patient does not take the buprenorphine as prescribed, try to identify the causes, and discuss measures for non-compliance with the patient for better patient care.

One way to do so might be patient education. Sublingual buprenorphine requires careful attention during intake. Some patients with low buprenorphine and norbuprenorphine levels might be swallowing the buprenorphine products. The package inserts of buprenorphine products describe the appropriate way to take the medication as follows: (1) hold buprenorphine under the tongue for 5 to 10 minutes until it is completely dissolved, (2) avoid drinking or eating while taking buprenorphine, and (3) discourage talking while holding buprenorphine sublingually.[21] In other words, sublingual buprenorphine should be placed under the tongue and held there without drinking, eating, or talking until it is completely dissolved, regardless of the drug packaging in a film or tablet form. Unless patients are in an environment such as halfway houses where administration of medications is closely observed, they might be taking buprenorphine carelessly or without knowing the correct way to take it. In these cases, providers could educate their patients on the appropriate way to take the medication.

Another reasonable measure when the urine norbuprenorphine-to-creatinine ratio is low could be discussing non-compliance with the patient, a possibility of forgetting to take the medication, or diversion. Despite efforts to

minimize medication diversion, patients in office-based opioid treatment centers often divert their buprenorphine reportedly.[9,22,23] Many OUD patients obtain diverted buprenorphine for reasons such as difficulty accessing legitimate treatment programs.[9,24] This kind of diversion is very difficult to discourage because it could help patients with OUD and possibly save them from overdose death.[25] Regardless of the reasons, providers should be aware of patients' non-compliance with their MAT. If any problematic behaviors are suspected, providers should discuss them with the patient to find their rationale. Those on diverted buprenorphine could be helped by providing them with an opportunity to engage in an appropriate treatment program, where their MAT will be structured for optimal patient care.

### *Limitations*

This study has several limitations; however, the primary one might be the data analysis power. We focused on urine samples from patients treated with 8 mg/day (n = 66), 12 mg/day (n = 83), and 16 mg/day (n = 35). A larger sample size would have increased the analysis power and therefore, the study validity, awaiting future research. Second, the maximum measurable levels of buprenorphine and norbuprenorphine at 2000 ng/mL might have made the analysis results inaccurate. Third, although patients in halfway houses were in a controlled environment, where their medications and their intake were monitored closely, non-compliance with the MAT by deceiving the staff was still possible; however, this manipulation was presumed very difficult. Fourth, this study did not include qualitative analysis; the providers' notes after each encounter were not examined. If this were done, the information could help to understand the dosage determining factors. Finally, this study did not consider the timing of buprenorphine intake in relation to urine collection. If some patients took buprenorphine within 7 hours before urine collection, their buprenorphine levels might have been high. However, this study was based on patients treated with buprenorphine for at least 6 days under staff supervision; the daily buprenorphine intake would have minimized the time factor effect, especially on norbuprenorphine levels.

## Conclusion

Routine urine testing is crucial for buprenorphine MAT programs because it could help buprenorphine prescribers identify non-prescribed substance use and non-adherence to the buprenorphine treatment. However, interpretation of the urine testing results could be complicated and thus, challenging. This retrospective study analyzed urine sample data from patients in halfway houses, where their medications were administered under close supervision, and suggested alarming features in urine testing results. This information could help buprenorphine prescribers interpret urine testing results more accurately, leading to better clinical decision-making, and optimal patient care in office-based buprenorphine MAT.

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## Author Contributions

All authors (HF, DS, RS, PE) contributed to the study conception and design, IRB application, data collection, data analysis, manuscript preparation, and/or revisions of the manuscript.

## Data Availability

The data used for this study is available upon request.

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