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Do buprenorphine doses and ratios matter in medication assisted treatment adherence?

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Abstract

Introduction: Buprenorphine (BUP), generally prescribed as buprenorphine/naloxone, is a key component of medication-assisted treatment (MAT) to manage opioid use disorder. Studies suggest higher doses of BUP increase treatment adherence. Routine urine drug screens (UDS) assist in monitoring MAT adherence via measurement of excreted BUP and its metabolite, norbuprenorphine (NBP). The clinical significance between BUP/NBP concentrations and their ratios for assessing adherence and substance use is not well-described.

Methods: We conducted a single-center, retrospective chart review of 195 clients age ≥18 years enrolled in a local MAT program from August 2017 to February 2021. Demographics, BUP doses, prescription history, and UDS results were collected. Participants were divided based on MAT adherence (<80% vs ≥80%) and median total daily dose (TDD) of BUP (≥16 mg vs <16 mg) in addition to pre- and post-COVID-19 cohorts.

Results: Median BUP/NBP urinary concentrations were significantly correlated with MAT adherence ($P < .0001$ for each) and a reduced percentage of positive UDS for opioids ($P = .0004$ and $P < .0001$, respectively) but not their ratios. Median TDD of BUP ≥16 mg (n = 126) vs <16 mg (n = 68) was not correlated with MAT adherence ($P = .107$) or incidence of nonprescription use ($P = .117$). A significantly higher incidence of UDS positive for opiates ($P = .049$) and alcohol ($P = .035$) was observed post-COVID-19.

Discussion: Clients appearing adherent to MAT who had higher concentrations of urinary BUP/NBP demonstrated a reduced incidence of opioid-positive UDS independent of the BUP dose prescribed. An increase in opioid- and alcohol-positive UDSs were observed during the COVID-19 pandemic.

Keywords: buprenorphine, norbuprenorphine, medication-assisted treatment, urine drug screen, urinary concentrations

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Introduction

Approximately 137 Americans die daily from prescription and nonprescription opioid overdose.[1] About 21% to 29% of patients prescribed opioids for chronic pain misuse them, and 8% to 12% develop an opioid use disorder (OUD).[2] Synthetic opioids, specifically nonprescription manufac-

tured fentanyl, contribute to the worsening of the opioid epidemic.[3] A driver of this spike in overdoses is an underlying SUD, which, like other chronic diseases, warrants appropriate treatment.[4]

Medication-assisted treatment (MAT) uses medications and counseling or behavioral therapies to treat SUDs with the goal of full recovery. MAT improves OUD treatment program retention, reduces inpatient detoxification services, decreases nonprescription opioid or opiate use and criminal activities, increases employment, and decreases morbidity and mortality.[5] In 2020, the American Society of Addiction Medicine guideline provided new and revised recommendations based on a targeted review of new evidence, FDA approval of new buprenorphine (BUP) formulations, and evolving clinical practice guidance for MAT.[6]

Whereas BUP, a high-affinity partial agonist at the μ-opioid receptor, can induce withdrawal symptoms by displacing other opioids, successful BUP induction results in craving reduction and attenuates the euphoric effects of other opiates or opioids.[6-8] Unlike full opioid agonists, BUP has a ceiling effect on respiratory depression.[9] Research identifies several factors impacting treatment retention and relapse rates when using BUP for OUD. Studies demonstrate that BUP doses ≥16 mg/d are associated with improved treatment retention and reduced nonprescription opioid or opiate use.[10,11] Other factors that improve MAT outcomes include longer treatment duration and higher program satisfaction.[10] Conversely, psychiatric comorbidities and nonopioid SUD, particularly methamphetamine use, reduce treatment retention.[12,13]

Routine urine drug screens (UDS) are recommended for all MAT programs to aid in recovery and improve patient outcomes.[14] BUP and its metabolite, norbuprenorphine (NBP), are excreted in the urine and detected in a UDS to assess treatment adherence. Whereas these concentrations have high intrapatient and interpatient variability, the measured ratios between BUP and NBP usually fall between 1:1 and 1:4.[15] Studies demonstrate that ratios <0.02 may indicate urine adulteration, a signal of nonadherence and potential substance diversion.[16,17] The clinical significance between BUP/NBP concentrations and their ratios for assessing adherence and substance use is not well-described.

Research into the impact of the COVID-19 pandemic on mental health reveals a 3- to 4-fold increase in the incidence of anxiety and/or depressive disorders along with increased substance use during COVID-19.[18-22] These changes are driven largely by social isolation; fear; income loss; housing instability; and reduced access to health care, medications, and supplies.[18-22] Individuals with an SUD are vulnerable in the postpandemic environment due to high rates of comorbid mental and physical health conditions.

The primary purpose of this study was to determine if urinary BUP/NBP concentrations and their ratios have a correlation with MAT adherence and substance use. Furthermore, this study explores whether total daily dose of BUP correlates with improved treatment adherence and reduced substance use as well as the impact of COVID-19 on the MAT population.

Methods

This IRB–approved study was a single-institution, retrospective chart review conducted on all MAT clients enrolled at Family Health Centers of San Diego (FHCSD) in collaboration with Scripps Mercy Hospital, San Diego, Department of Pharmacy, using FHCSD electronic health records dated from August 1, 2017 to February 28, 2021. All eligible participants in the MAT program were included if they were ≥18 years old with at least 2 UDS results postinduction with film BUP only. Variables collected include demographics, prescription fill history, concomitant psychiatric diagnoses and medications, OUD background (eg, previous MAT use, preferred opioid of choice), and all UDS results during MAT enrollment. Participants were excluded if they were receiving MAT products other than film BUP.

Clients were divided into cohorts based on MAT adherence and nonadherence, defined as clients who obtained their MAT prescriptions ≥80% and <80% of the time, respectively. BUP prescription records were obtained based on the statewide prescription drug monitoring program for controlled substances and validated with dispensing outpatient pharmacies. Adherence was calculated by dividing the sum total daily supply of BUP by the total days between the first and last prescriptions written multiplied by 100. Clients were further divided into high- (≥16 mg/d) and low-dose (<16 mg/d) BUP cohorts calculated by the median total daily dose of BUP prescribed throughout MAT enrollment. Urinary BUP/NBP concentrations (nanograms per milliliter) were normalized to (divided by) urine creatinine (milligrams per milliliter) obtained in the same urine sample to account for interclient variability of urine concentrations between UDS samples.[23] Median intrapatient values of normalized BUP/NBP concentrations and NBP:BUP ratios were then calculated for analysis of outcomes. Substance use was defined as a positive UDS for non-BUP drugs of misuse at any time during MAT enrollment, excluding the initial induction period. An exploratory analysis was performed on a subgroup of clients with at least one UDS result before and after March 13, 2020 (the date of the declaration of national emergency in the United States, referred to as pre- and post-COVID-19, respectively) for substance use and MAT program retention.

The primary study outcome was to determine whether urinary BUP/NBP concentrations and ratios were correlated with MAT adherence and substance use. The secondary study outcome was to explore whether patients prescribed higher median total daily BUP (≥16 mg/d vs <16 mg/d) had improved treatment adherence and/or reduced substance use. Finally, an exploratory analysis was performed to examine the impact of COVID-19 on the MAT population.

Descriptive statistics evaluated demographics and baseline characteristics. Continuous variables were expressed as a mean ± SD for normally distributed data and median ± IQR for nonparametric data. Differences in substance use and adherence based on BUP dose was calculated via chi-squared test. Correlation measures were calculated using the Pearson correlation test to determine an association between normalized median BUP/NBP concentrations and ratios with adherence and percentage of all UDS positive for non-BUP substances. A paired two-tailed *t* test was used to compare UDS results in the pre- and post-COVID-19 subgroup. A *P* value <.05 was considered statistically significant for all outcomes.

Results

A total of 231 clients were screened. Twenty-five clients had fewer than two UDS postinduction, and 11 were treated with non-BUP products, leaving 195 eligible clients. Baseline demographics were similar between MAT adherent (n = 154) and MAT nonadherent (n = 41) clients (Table 1). Most clients were white, non-Hispanic males. More than 89% of clients had at least one comorbid SUD, and 80% had at least one comorbid psychiatric disorder. Clients continuing MAT at the time of enrollment (eg, transferred services from another MAT program) were significantly more adherent versus newly initiated MAT clients (63.6% vs 46.3%, $P = .045$) as were clients who preferred prescription opioids (eg, oxycodone) compared with those who preferred heroin or nonprescription manufactured fentanyl (89.9% vs 73%, $P = .006$).

Normalized median BUP/NBP urinary concentrations were significantly correlated with MAT adherence (Figure; BUP: $(r)193 = .3084$, $P < .0001$; NBP: $(r)193 = .3238$, $P < .0001$). The median ratios of NBP:BUP did not correlate with adherence ($(r) = .0423$; $P = .558$). A statistically significant negative correlation between normalized median BUP/NBP urinary concentrations and percentage of positive UDS for opioids (BUP: $(r)193 = -.2537$, $P = .0004$; NBP: $(r) = -.326$, $P < .001$) was seen. The median total daily dose of BUP ≥16 mg versus <16 mg did not correlate with MAT adherence ($P = .107$; Table 1) or incidence of substance use (Table 2). In a post hoc analysis, the incidence of positive UDS for multiple substances was significantly lower in the MAT adherent versus nonadherent cohort, including opioids (39.6% vs 68.3%, $P = .001$), stimulants (32.5% vs 61%, $P < .001$), and ethanol metabolites (36.4% vs 53.7%, $P = .045$). One client in the MAT adherent cohort was excluded due to an insufficient number of BUP prescriptions filled to calculate adherence. Of 2339 UDS samples analyzed, only 6 had NBP:BUP ratios <0.02, suggestive of possible adulteration in 5 clients.

For a subgroup of clients enrolled both pre- and post-COVID-19 with at least one UDS, a significantly higher incidence of positive UDS for opiates and alcohol were observed post-COVID-19 (Table 3). Within the post-COVID-19 time frame, the frequency of UDS collection decreased from a median of every 14.4 days (IQR 10.2 to 22.8) to every 30 days (IQR 11.5 to 66.7). For all clients enrolled at the start of the COVID-19 pandemic (n = 89), 38.2% (n = 34) discontinued treatment within the following year. Of the clients who discontinued treatment, 76.4% (n = 26) were either lost to follow-up or voluntarily withdrew from the program, and 61.8% (n = 21) discontinued without having a UDS collected in the post-COVID-19 time frame.

Discussion

To our knowledge, this is the first study to investigate the potential significance of BUP/NBP concentrations and their ratios for adherence and substance use outside the context of urine adulteration and/or diversion. Results suggest that normalized urinary concentrations of BUP/NBP but not their ratios correlate with increased MAT adherence and reduced incidence of opioid-positive UDS. This finding is independent of prescribed BUP dose (≥16 mg vs <16 mg), which, in contrast to the findings of previous studies, did not significantly correlate with MAT adherence or nonprescription drug use. Together, these results suggest that urinary concentrations of BUP/NBP may provide clinical utility beyond monitoring MAT adherence. Evidence of urine adulteration and potential medication diversion was exceedingly rare with NBP:BUP ratios of <0.02 present in less than 0.26% of urine samples analyzed. A post hoc analysis revealed that comorbid stimulant (predominantly methamphetamine) opiate/opioid, and alcohol use during treatment correlated significantly with reduced MAT adherence similarly to findings of previous studies.

In a subpopulation of MAT clients enrolled both pre- and post-COVID-19, the incidence of UDS positive for non-BUP opioids doubled from 5.3% to 10.6% pre- versus post-COVID-19, respectively. A 1.5-fold increase in the incidence of UDS positive for ethanol metabolites was also observed in this population. This finding was seen despite a reduction in the UDS collection rate of more than 50% during the post-COVID-19 time frame with many clients seen through

TABLE 1: Client demographics of the study

Client Characteristic[a]	MAT Adherent, n = 154	MAT Nonadherent, n = 41	Total, N = 195	*P* Value
Average age, mean ± SD	40.67 ± 10.84	38.98 ± 10.26	40.31 ± 10.72	.370
Gender				.228
Male	102 (66.2)	32 (78)	134 (68.7)	
Female	52 (33.8)	9 (22)	61 (31.3)	
Ethnicity				.052
Non-Hispanic	98 (63.6)	20 (48.8)	118 (60.5)	
Hispanic	38 (24.7)	18 (43.9)	56 (28.7)	
Unknown	18 (11.7)	3 (7.3)	21 (10.8)	
Race				.578
White	117 (76)	28 (68.3)	145 (74.4)	
African American	7 (4.5)	2 (4.9)	9 (4.6)	
Other or declined	30 (19.5)	11 (26.8)	41 (21)	
Comorbid psychiatric diagnosis	123 (79.9)	33 (80.5)	156 (80)	.93
Schizophrenia	7 (4.5)	1 (2.4)	8 (4.1)	.751
Bipolar disorder	24 (15.6)	4 (9.8)	28 (14.4)	
Depression	99 (64.3)	28 (68.3)	127 (65.1)	
Anxiety	83 (53.9)	20 (48.8)	103 (52.8)	
Comorbid SUD	135 (87.7)	39 (95.1)	174 (89.2)	.171
Alcohol use	76 (49.4)	23 (56.1)	99 (50.8)	.714
Cannabis use	73 (47.4)	21 (51.2)	94 (48.2)	
Stimulant use	103 (66.9)	37 (90.2)	140 (71.8)	
Other	90 (58.4)	23 (56.1)	113 (57.9)	
Preferred opioid—non-Rx	92 (52.7)	34 (82.9)	126 (64.6)	.006[b]
Preferred opioid—Rx	62 (40.3)	7 (17.1)	69 (35.4)	
Continuation of MAT—Yes	98 (63.6)	19 (46.3)	117 (60)	.045[b]
Emergency department Rx	31 (20.1)	6 (14.6)	37 (19)	.191
Other MAT clinic or PCP	56 (36.4)	8 (19.5)	64 (32.8)	
Nonprescription use or purchase	11 (7.1)	5 (12.2)	16 (8.2)	
Previous use of MAT	118 (76.6)	31 (75.6)	149 (76.4)	.892
Median BUP dose, No. (IQR)	16 (12,20)	16 (12,20)	16 (12,20)	.500
BUP total daily dose ≥16 mg	95 (62.1)	31 (75.6)	126 (64.9)	.107
BUP total daily dose <16 mg	58 (37.9)	10 (24.4)	68 (35.1)	

BUP = buprenorphine; MAT = medication-assisted treatment; PCP = primary care physician.

[a]Values presented as No. (%) unless otherwise noted.

[b]Value was clinically significant.

TABLE 2: Median buprenorphine (BUP) total daily dose and positive urine drug screen results[a]

Positive Urine Culture	BUP Total Daily Dose ≥16 mg, n = 125, No. (%)	BUP Total Daily Dose <16 mg, n = 70, No. (%)	All BUP Doses, N = 195, No. (%)	*P* Value
Opiates	62 (49.6)	27 (38.6)	89 (45.6)	.138
Stimulants	54 (43.2)	21 (30)	75 (38.5)	.069
Ethanol	54 (43.2)	24 (34.3)	78 (40)	.223
Marijuana metabolites	73 (58.4)	33 (47.1)	106 (54.4)	.130
Any positive result	106 (84.8)	53 (75.7)	159 (81.5)	.117

[a]All available urine drug screen during treatment period were used.

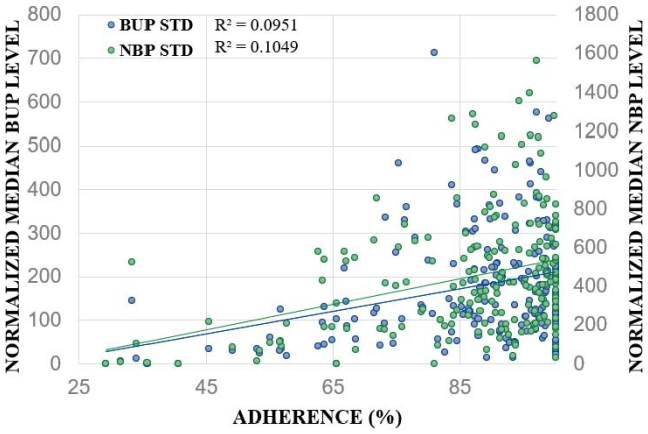

FIGURE: Normalized median buprenorphine (BUP) and norbuprenorphine (NBP) concentrations versus adherence (n = 194; STD = standard deviation)

telehealth for multiple months without an in-person clinic visit. More than 60% of patients who discontinued treatment post-COVID-19 had their UDS collected prior to the lockdown date, which may minimize the true magnitude of substance use and relapse during this period. A similar reduction in UDS testing and increase in incidence of opioid-positive UDS is described in the non-MAT population post-COVID-19.[24] The treatment discontinuation rate approached 40% in the year following California's first statewide stay-at-home order, almost double the historical 1-year retention rate of 80% at this MAT program.

Limitations of this study include the single-center, retrospective design that is unable to determine causality. The data were not inclusive of all potential mediators of MAT adherence and are limited by potential documentation bias. Also, despite collecting more than 3500 prescription fill records to calculate adherence, this method may not reflect real-world medication use. Furthermore, laboratory results of BUP/NBP UDS concentrations had an upper threshold for measurement, limiting the validity of NBP:BUP ratios for clients, who frequently exceeded the thresholds, and potentially attenuating the magnitude of the correlation between adherence and BUP/NBP concentrations. As previously noted, available UDS data was significantly reduced in the months immediately following the initial COVID-19 lockdown, potentially underestimating the magnitude of substance use in the pre- versus post-COVID-19 cohort. Finally, institutional prescribing practices promoting liberal dose increases in BUP for more treatment-resistant patients is a major confounding variable that limits the validity of findings as they relate to total daily dose of BUP.

TABLE 3: Pre- versus post-COVID-19 urine drug screen results (n = 70)

Positive Urine Culture	Pre-COVID-19, %	Post-COVID-19, %	*P* Value
Opiates	5.3	10.6	.049[a]
Stimulants	15.3	20.3	.133
Ethanol	13.4	20.1	.035[a]
Marijuana metabolites	32.1	35.4	.298
Any positive result	52.8	59.6	.130

[a]Value was clinically significant.

In summary, this study shows a correlation between higher BUP/NBP urinary concentrations and MAT adherence in addition to reduced non-BUP opioid use. This finding is independent of the dose of BUP prescribed (high- vs low-dose), which did not significantly correlate with either MAT adherence or substance use. Increased incidence of non-BUP opioid and alcohol use was observed in a subgroup of the FHCSD MAT cohort post-COVID-19 despite reduction in UDS testing and the high treatment discontinuation rate before more routine UDS collection resumed. Further research is necessary to determine if/how BUP/NBP concentrations can be utilized as a method to assist clinicians in improving MAT adherence and retention plus identify barriers to care, other factors that impact treatment program retention, and increased incidence of substance use in the MAT population during the COVID-19 pandemic.

References

1. National Institute on Drug Abuse [Internet]. Overdose death rates [published 2021 Jan 29; cited 2021 Jul 9]. Available from: https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates
2. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain. Pain. 2015;156(4):569-76. DOI: 10.1097/01.j.pain.0000460357.01998.f1. PubMed PMID: 25785523.
3. Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 National Survey on Drug Use and Health. Ann Intern Med. 2017;167(5):293-301. DOI: 10.7326/M17-0865. PubMed PMID: 28761945.
4. Weiner SG, El Ibrahimi S, Hendricks MA, Hallvik SE, Hildebran C, Fischer MA, et al. Factors associated with opioid overdose after an initial opioid prescription. JAMA Netw Open. 2022;5(1):e2145691. DOI: 10.1001/jamanetworkopen.2021.45691. PubMed PMID: 35089351; PubMed Central PMCID: PMC8800077.
5. Substance Abuse and Mental Health Services Administration [Internet]. Medication-assisted treatment (MAT) [cited 2021 Jul 9]. Available from: https://www.samhsa.gov/medication-assisted-treatment
6. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015;9(5):358-67. DOI: 10.1097/ADM.0000000000000166. PubMed PMID: 26406300; PubMed Central PMCID: PMC4605275.
7. Suboxone (buprenorphine) [prescribing information]. Richmond: Indivior.
8. Bart G. Maintenance medication for opiate addiction: the foundation of recovery. J Addict Dis. 2012;31(3):207-25. DOI:

10.1080/10550887.2012.694598. PubMed PMID: 22873183; PubMed Central PMCID: PMC3411273.
9. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994;55(5):569-80. DOI: 10.1038/clpt.1994.71. PubMed PMID: 8181201.
10. Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend. 2014;144:1-11. DOI: 10.1016/j.drugalcdep.2014.07.035. PubMed PMID: 25179217.
11. Herring A, Vosooghi AA, Luftig J, Anderson ES, Zhao X, Dziura J et al. High-dose buprenorphine induction in the emergency department for treatment of opioid use disorder. JAMA Netw Open. 2021;4(7):e2117128. doi:10.1001/jamanetworkopen.2021.17128. PubMed PMID: 34264326; PubMed Central PMCID: PMC8283555.
12. Tsui JI, Mayfield J, Speaker EC, Yakup S, Ries R, Funai H, et al. Association between methamphetamine use and retention among patients with opioid use disorders treated with buprenorphine. J Subst Abuse Treat. 2020;109:80-5. DOI: 10.1016/j.jsat.2019.10.005. PubMed PMID: 31810594.
13. Samples H, Williams AR, Olfson M, Crystal S. Risk factors for discontinuation of buprenorphine treatment for opioid use disorders in a multi-state sample of Medicaid enrollees. J Subst Abuse Treat. 2018;95:9-17. DOI: 10.1016/j.jsat.2018.09.001. PubMed PMID: 30352671; PubMed Central PMCID: PMC6354252.
14. Jarvis M, Williams J, Hurford M, Lindsay D, Lincoln P, Giles L, et al. Appropriate use of drug testing in clinical addiction medicine. J Addict Med. 2017;11(3):163-73. DOI: 10.1097/ADM.0000000000000323. PubMed PMID: 28557958.
15. Hull MJ, Bierer MF, Griggs DA, Long WH, Nixon AL, Flood JG. Urinary buprenorphine concentrations in patients treated with Suboxone(R) as determined by liquid chromatography-mass spectrometry and CEDIA immunoassay. J Anal Toxicol. 2008;32(7):516-21. DOI: 10.1093/jat/32.7.516. PubMed PMID: 18713521.
16. Holt SR, Donroe JH, Cavallo DA, Tetrault JM. Addressing discordant quantitative urine buprenorphine and norbuprenorphine levels: case examples in opioid use disorder. Drug Alcohol Depend. 2018;186:171-4. DOI: 10.1016/j.drugalcdep.2017.12.040. PubMed PMID: 29579725.
17. Warrington JS, Warrington GS, Francis-Fath S, Brooklyn J. Urinary buprenorphine, norbuprenorphine and naloxone concentrations and ratios: review and potential clinical implications. J Addict Med. 2020;14(6):e344-9. DOI: 10.1097/ADM.0000000000000676. PubMed PMID: 32530884.
18. Czeisler M, Lane RI, Petrosky E, Wiley JF, Christensen A, Njai R, et al. Mental health, substance use, and suicidal ideation during the COVID-19 pandemic–United States, June 24-30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(32):1049-57. DOI: 10.15585/mmwr.mm6932a1. PubMed PMID: 32790653; PubMed Central PMCID: PMC7440121.
19. Panchal N, Kamal R. The implications of COVID-19 for mental health and substance use [Internet]. San Francisco: KFF [published 2021 Feb 10; cited 2021 Jul 9]. https://www.kff.org/coronavirus-covid-19/issue-brief/the-implications-of-covid-19-for-mental-health-and-substance-use/.
20. Grunvald W, Herrington R, King R, Lamberson M, Mackey S, Maruti S et al. COVID-19: a new barrier to treatment for opioid use disorder in the emergency department. J Am Coll Emerg Physicians Open. 2021;2(2):e12403. DOI: 10.1002/emp2.12403. PubMed PMID: 33748808.
21. Jenkins WD, Bolinski R, Bresett J, Van Ham B, Fletcher S, Walters S, et al. Commentary: COVID-19 during the opioid epidemic–exacerbation of stigma and vulnerabilities. J Rural Health. 2021;37(1):172-4. DOI: 10.1111/jrh.12442. PubMed PMID: 32277731.
22. Henderson R, McInnes A, Mackey L, Bruised Head M, Crowshoe L, Hann J, et al. Opioid use disorder treatment disruptions during the early COVID-19 pandemic and other emergent disasters: a scoping review addressing dual public health emergencies. BMC Public Health. 2021;21(1):1471. DOI: 10.1186/s12889-021-11495-0. PubMed PMID: 34320954; PubMed Central PMCID: PMC8318046.
23. Adedeji AO, Pourmohamad T, Chen Y, Burkey J, Betts CJ, Bickerton SJ, et al. Investigating the value of urine volume, creatinine, and cystatin C for urinary biomarkers normalization for drug development studies. Int J Toxicol. 2019;38(1):12-22. DOI: 10.1177/1091581818819791. PubMed PMID: 30673360.
24. Niles JK, Gudin J, Radcliff J, Kaufman HW. The opioid epidemic within the COVID-19 pandemic: drug testing in 2020. Popul Health Manag. 2021;24(S1):S43-51. DOI: 10.1089/pop.2020.0230. PubMed PMID: 33031013; PubMed Central PMCID: PMC7875135.