BRIEF COMMUNICATION

Monitoring buprenorphine in patients on medication-assisted treatment

Amadeo Pesce, PhD; Katie Bollman, BA; Kevin Krock, PhD; Agnes Cua, PhD; Keith Tran, BS; Richard Thomas, PhD

ARTICLE INFO

Keywords:
buprenorphine
norbuprenorphine
naloxone
urine drug testing
oral fluid drug testing

DOI:10.5055/jom.0844

ABSTRACT

Background: *Buprenorphine is used for medication-assisted treatment of opioid dependence.*
Purpose: *Monitoring of medication adherence involves testing of urine or oral fluid for the drug or its metabolite.*
Methods: *Quantitative results using liquid chromatography tandem mass spectrometer testing defined the excretion pattern of the drug and its metabolites.*
Results: *Frequency distribution curves of buprenorphine and norbuprenorphine describe the expected drug concentrations of patients on this medication.*
Conclusion: *Urine and oral fluid drug testing can be used to monitor adherence in this population.*

BACKGROUND

Buprenorphine is a partial opioid agonist used to treat pain but also used for medication-assisted treatment for opioid dependence. The most common prescription is for Suboxone™,[1] which is a film that releases the drug in a sublingual manner. This formulation is in the top 100 prescribed medications (*https://rxsaver.retailmenot.com/top-100-drugs-lists/*).[2] This dosage method is used because the drug is subjected to first pass liver metabolism where it is rendered ineffective by glucuronidation and dealkylation. By using sublingual administration, the first pass metabolism is mitigated. This dosage form also contains naloxone, a potent opiate reversal agent used to prevent misuse of the buprenorphine by injection. Commonly, this medication contains buprenorphine to naloxone ratio of four parts buprenorphine to one part naloxone (4 mg buprenorphine to 1 mg naloxone). The drug is metabolized and appears in urine as buprenorphine parent drug, buprenorphine glucuronide, norbuprenorphine, and norbuprenorphine glucuronide.

The pharmacokinetics are well described.[3] In addition, the NIH has listed a number of guidelines for prescribers.[4-8] Studies have shown that medication adherence can be appropriately monitored using urine drug testing.[9-13] In addition, Furo et al. have shown a good correlation between the buprenorphine dose and the amount of the drug found in urine, thus demonstrating that this is a valid method of showing medication adherence.[14,15]

METHODS

Treating providers use urine or oral fluid drug testing to determine if the patient is taking the medication as prescribed. Some laboratories monitor the urine buprenorphine and norbuprenorphine after treatment of the urine with glucuronidase, while others monitor the buprenorphine norbuprenorphine and their glucuronide metabolites. Our laboratory only monitors the urinary buprenorphine and norbuprenorphine after removal of the glucuronide moieties using KURA b-glucuronidase.[16] The test drugs are separated by chromatography using an InfinityLab Poroshell 120 PhenylHexyl Column, 2.7 µm, 4.6 × 50 mm, using 0.1 percent formic acid, and 80 percent methanol at 5-minute gradient. The m/z values for monitoring buprenorphine,

norbuprenorphine, and naloxone are presented in Table 1.

One of the differences between laboratories is their method of measurement and the concentration at which they will call the test positive for the presence of the drug. The cutoff values for our laboratory are presented in Table 2. The methods of selecting the appropriate cutoff have been previously described.[17-19]

Between January 2, 2020, and July 25, 2023, we received 1,548,558 urine specimens collected at the providers site to be tested for buprenorphine, norbuprenorphine, and naloxone. These were from pain management practices and rehabilitation facilities.[20] We tested 23,332 oral fluid specimens for buprenorphine, norbuprenorphine, and naloxone. The methods of collection have been previously described.[21,22] We have previously published some of our observations on the ratio of norbuprenorphine to buprenorphine. These were recalculated to demonstrate the attempts at deception to show buprenorphine use consistent with prescription use.

RESULTS

Of these tested specimens, 553,349 were positive for buprenorphine with a median concentration of 176 ng/mL, 552,952 were positive for norbuprenorphine with a median concentration of 449 ng/mL, and 264,683 were positive for naloxone with a median concentration of 492 ng/mL. We tested 233,332 oral specimens for buprenorphine. The median concentration was 124 ng/mL, and of the 13,477 specimens positive for norbuprenorphine, the median concentration was 16 ng/mL. Clearly there is a difference between the two matrices, urine and oral fluid.[22]

DISCUSSION

Questions commonly asked about the urine monitoring for buprenorphine include "is the buprenorphine concentration too high?" and "is the concentration consistent with the dose?" It is not possible to answer these questions based solely on the concentration values. In general, one cannot correlate the prescription dosage and the amount of drug excreted. One must consider both the parent drug and its metabolite norbuprenorphine concentrations. Usually, the presence of norbuprenorphine is consistent with the patient taking the drug, since metabolism is the only source of the compound. Contrary to some of the information on the internet, norbuprenorphine is not from a medication impurity. Our experience is that when buprenorphine is present, norbuprenorphine is also present 98.3 percent of the time. Use of frequency distribution data can be useful for interpretation. These are presented in Figures 1 and 2. In general, more of the metabolite is observed than the parent drug. The median concentration of the excreted buprenorphine was 176 ng/mL, while that of the norbuprenorphine was 492 ng/mL. In the case of the oral fluid specimens, the buprenorphine concentrations were much greater than those of the norbuprenorphine. The frequency distribution curves for the oral fluid data can be approximated to follow a Gaussian distribution after a log transformation.[17-19] However, this was

Table 1. Mass ions used in LC-MS/MS testing

	Buprenorphine	Norbuprenorphine	Naloxone	Buprenorphine oral	Norbuprenorphine	Naloxone
Internal standard	Buprenorphine D4	Norbuprenorphine D3	Naloxone D5	Buprenorphine D4	Norbuprenorphine D3	Naloxone D5
Parent ion, m/z	468.2	414.2	328.1	468.2	414.2	328.1
Qualifier ion, m/z	396.2	187	253	396.2	187	253
Quantifier ion, m/z	414.2	83	212	414.2	83	212
Retention time (minutes)	2.32	2.15	2.15	3.1	2.84	1.85

Table 2. Cutoff values	
Drug	**Cutoff values**
Buprenorphine in urine	5 ng/mL
Norbuprenorphine in urine	5 ng/mL
Naloxone in urine	10 ng/mL
Buprenorphine in oral fluid	0.3 ng/mL
Norbuprenorphine in oral fluid	5.0 ng/mL
Drug	**Buprenorphine**
N conc. 1-100	23,436
Log median M/P	0.600 (4.0)
Outliers	297
Outliers (percent)	1.27
N conc. 100-500	36,648
Log median M/P	0.432 (2.7)
Outliers	536
Outliers (percent)	1.46
N conc. 500-1,000	9,769
Log median M/P	0.246 (1.76)
Outliers	229
Outliers (percent)	2.34
N conc. 1,000-5,000	4,429
Log median M/P	0.050 (1.12)
Outliers	314
Outliers (percent)	7.09
N conc. 5,000-10,000	317
Log median M/P	–2.40 (0.004)
Outliers	32 (not true)
Outliers (percent)	10.09 ~all
N conc. above 10,000	401
Log median M/P	–2.645 (0.005)
Outliers	16 (not true)
Outliers (percent)	3.99 ~all

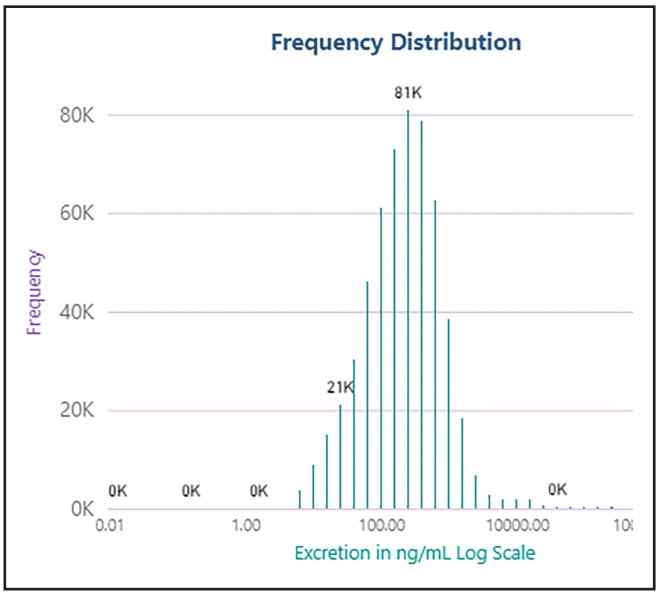

Figure 1. Distribution frequency of buprenorphine in urine specimens.

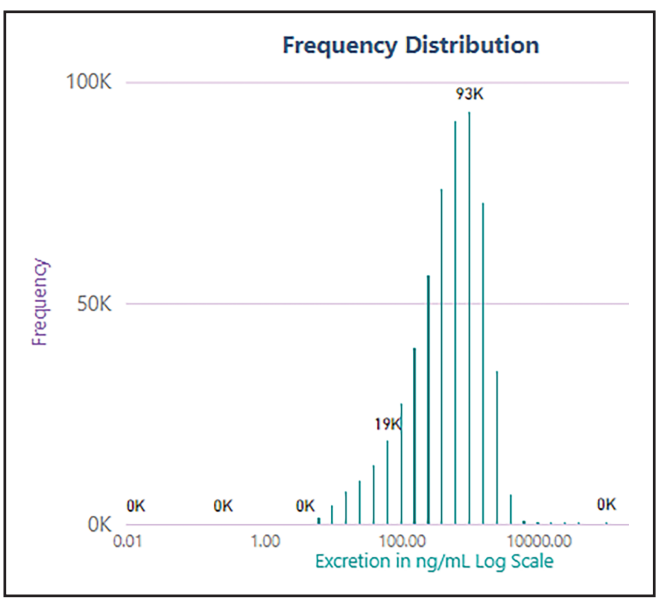

Figure 2. Distribution frequency of norbuprenorphine in urine specimens.

not possible for the oral fluid buprenorphine data. There seems to be a disproportionate number of specimens with high buprenorphine concentrations. We attribute these observations to poor oral hygiene prior to giving the oral fluid specimen caused by residual buprenorphine from the Suboxone film. The norbuprenorphine appears to follow the expected Gaussian curvature. This metabolite is not influenced by residual film buprenorphine.

One common question is how long after a dose can the drug be detected? For buprenorphine and its

metabolite, this is estimated to be 1-6 days. Using the frequency distribution data, the provider can estimate where the specific patient falls with respect to others in this group. The usual interpretation is that very high concentrations indicate overuse and that very low concentrations indicate that the drug was taken at a longer time interval than that prescribed. One other piece of information used to assess compliance is the norbuprenorphine to buprenorphine ratio. In general, the norbuprenorphine concentration is higher than that of the buprenorphine. Low ratios of buprenorphine to norbuprenorphine are consistent with an end of dose relationship. High buprenorphine to norbuprenorphine ratios (greater than 10 to 1) usually indicate an attempt to alter the drug test, commonly by adding the parent drug to the test specimen.[23,24] One of the concerns of the provider when low norbuprenorphine to buprenorphine ratios are observed is that this may be due to a metabolic deficiency. We usually discount this explanation as this is a rare possibility. Another explanation used by patients is that the drug was a contaminant of their current medication. A recent article on drug testing discounts this possibility.[4]

If the patient is taking Suboxone and if the laboratory also tests for naloxone, the detection of its presence and its concentration in urine can help with the urine drug test interpretation. Naloxone is rapidly metabolized to its glucuronide metabolite, and this is the major metabolite observed in urine. Our laboratory treats the urine with glucuronidase and measures the parent drug concentration. The frequency distribution curve is presented in Figure 3. We observed that naloxone was present in about 57 percent of the tested urine samples. The median concentration was 414 ng/mL.

We noted that at urine concentrations greater than 5,000 ng/mL there generally is a proportionately much lower concentration of norbuprenorphine, leading us to believe that these specimens were from individuals practicing deception by dipping the medication formulation into the urine collection cup. Our previous analysis was flawed because all of the low norbuprenorphine/buprenorphine data were included in the statistical analysis.

Some medical practices use oral fluid testing to monitor buprenorphine. The frequency distribution curves of the observed buprenorphine concentrations are presented in Figure 4. In general, these are considerably lower than the urine concentrations. The large difference between the two matrices

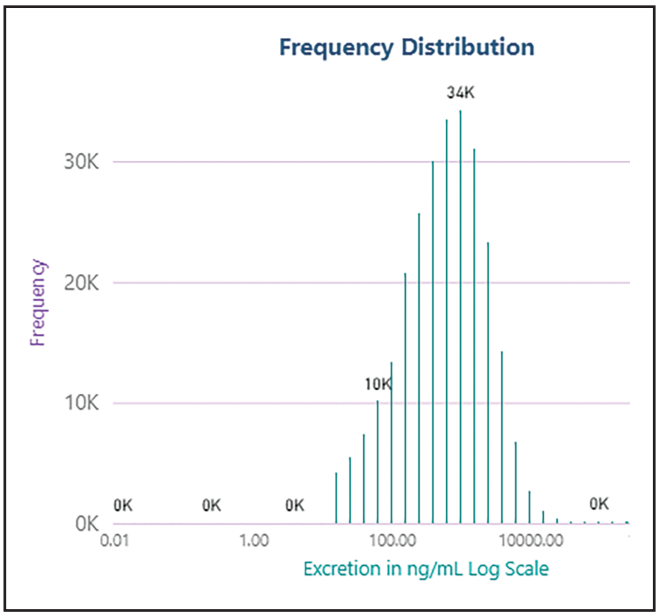

Figure 3. Distribution frequency of naloxone in urine specimens.

is that norbuprenorphine is present only 27 percent of the time. It is also present in lower quantities (Figure 5) with a median value of 15 ng/mL compared to 83 ng/mL for buprenorphine. This is explained by the metabolism of norbuprenorphine. As it is mostly glucuronidated, this form of the drug does not pass through the oral membranes and into oral fluid itself, whereas not all of the parent drug is glucuronidated and thus able to enter the oral cavity. One of the caveats of using oral fluid to monitor

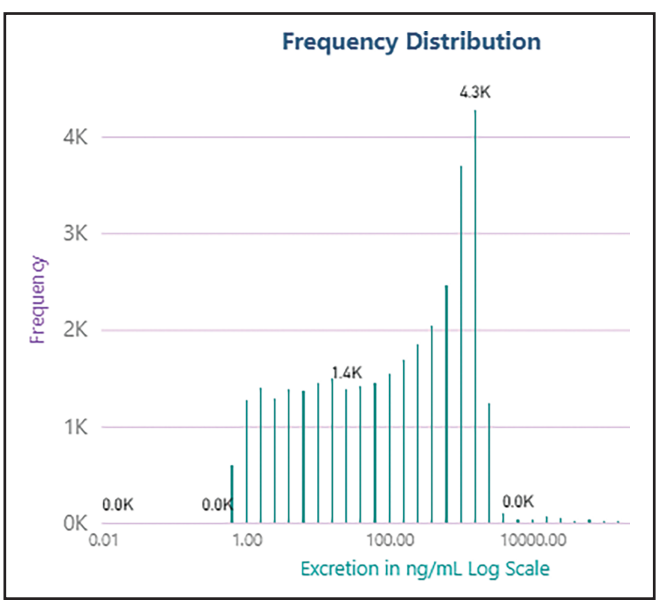

Figure 4. Distribution frequency of buprenorphine in oral fluid specimens.

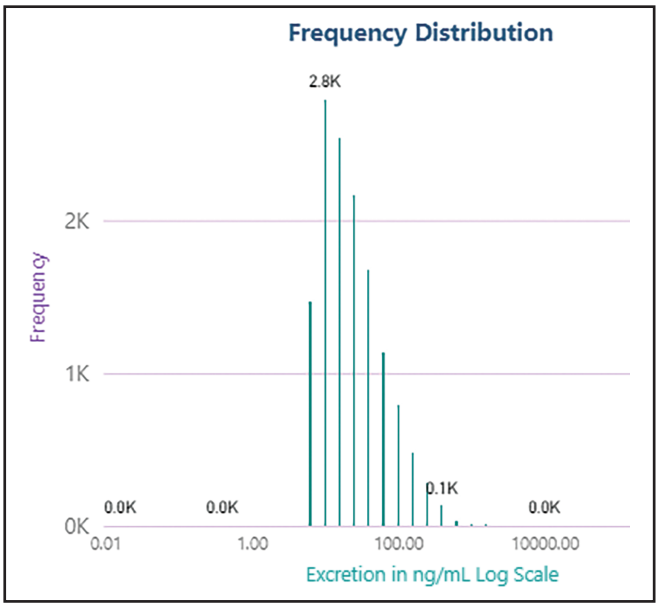

Figure 5. Distribution frequency of norbuprenorphine in oral fluid specimens.

Suboxone is that patients may not have flushed out all the buprenorphine containing film. In these cases, we observe very high buprenorphine concentrations with a very low concentration of norbuprenorphine.

Some physician practices use point-of-care devices to test for medication adherence. One must be aware of the difference between this type of test device and the definitive testing performed by most reference laboratories using liquid chromatography tandem mass spectrometer (LC–MS/MS) technology. The major difference is the cutoff. LC–MS/MS testing often uses lower cutoffs to establish compliance. A second major difference is that point-of-care devices often do not detect norbuprenorphine. Thus, a patient may test negative on the point-of-care test device and be positive by the LC–MS/MS test.

CONCLUSION

In order to observe the presence of buprenorphine and or norbuprenorphine in urine and use a measurement cutoff of 10 ng/mL, the patient must have taken a dose of drug in the 1-4 mg range.[14,15] If the patient tests negative for these analytes, the first conclusion is that the patient is not compliant with the prescribed medications. For this reason, patients on the Butrans™ patch often test negative in urine and oral fluid drug testing. In one formulation, the Butrans patch[25] releases about 10 µg/h or about 240 µg/day. This is about one twentieth of the 4 mg/from one Suboxone film. Most often the amount excreted from this patch is below the cutoff of the laboratory's test system and the urine or oral fluid test result is reported as negative.

Amadeo Pesce, PhD, Precision Diagnostics LLC, San Diego, California. ORCID: https://orcid.org/0000-0003-3748-9703.

Katie Bollman, BA, Precision Diagnostics LLC, San Diego, California.

Kevin Krock, PhD, Precision Diagnostics LLC, San Diego, California.

Agnes Cua, PhD, Precision Diagnostics LLC, San Diego, California.

Keith Tran, BS, Precision Diagnostics LLC, San Diego, California.

Richard Thomas, PhD, Precision Diagnostics LLC, San Diego, California.

REFERENCES

1. Suboxone Uses Dosage Side Effects and Warnings Drugs: Available at *https://www.drugs.com/suboxone.html.com*. Accessed January 12, 2024.

2. RxSaver Editors Top 100 most commonly searched medications: Available at *https://rxsaver.retailmenot.com/top-100-drugslists/*. Accessed January 12, 2024.

3. Elkader A, Sproule B: Buprenorphine: Clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet.* 2005; 44(7): 661-680. DOI: 10.2165/00003088-200544070-00001.

4. Pergolizzi J, Böger RH, Budd K, et al.: Sacerdote opioids and the management of chronic severe pain in the elderly: Consensus statement of an international expert panel with focus on the six clinically most often used World Health Organization step iii opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract.* 2008; 8(4): 287-313. DOI: 10.1111/j.1533-2500.2008.00204.x.

5. Kumar R, Viswanath O, Saadabadi A: *StatPearls [Internet].* Treasure Island, FL: StatPearls Publishing, 2023. Available at *https://www.ncbi.nlm.nih.gov/books/NBK459126/*. Accessed January 12, 2024.

6. Preuss CV, Kalava A, King KC: Prescription of controlled substances: Benefits and risks. In *StatPearls [Internet].* Treasure Island, FL: StatPearls Publishing, 2023. Available at *https://nmbs.cloud-cme.com/assets/nmbs/Presentations/1281/1281.pdf.* Accessed January 12, 2024.

7. Horn DB, Vu L, Porter BR, et al.: Responsible controlled substance and opioid prescribing. In *StatPearls [Internet].* Treasure Island, FL: StatPearls Publishing, 2023.

8. Dydyk AM, Sizemore DC, Haddad LM, et al.: NP safe prescribing of controlled substances while avoiding drug diversion. In *StatPearls [Internet].* Treasure Island, FL: StatPearls Publishing, 2023.

9. Cohen AN, Collins G, Nucifora FC, Jr, et al.: Clinical consensus recommendations for urine testing of adherence to antipsychotics

among people with serious mental illness. *Psychiatric Serv.* 2018; 69: 345-348. DOI: 10.1176/appi.ps.201700082.

10. Kavanagh K, Tallian K, Sepulveda JA, et al.: Do buprenorphine doses and ratios matter in medication assisted treatment adherence? *Ment Health Clin.* 2022; 12(4): 241-246. DOI: 10.9740/mhc.2022.08.241.

11. Kovar L, Schräpel C, Selzer D, et al.: Physiologically-based pharmacokinetic (PBPK) modeling of buprenorphine in adults, children and preterm neonates. *Pharmaceutics.* 2020; 12: 578. DOI: 10.3390/pharmaceutics12060578.

12. Warrington JS, Warrington GS, Francis-Fath S, et al.: Urinary buprenorphine, norbuprenorphine and naloxone concentrations and ratios: Review and potential clinical implications. *Addict Med.* 2020; 14: e344-e349. DOI: 10.1097/ADM.0000000000000676.

13. Anderson PL: Commentary: What can urine tell us about medication adherence? *EClinicalMedicine.* 2018; 22-28. DOI: 10.1016/j.eclinm.2018.08.004.

14. Furo H, Wiegand T, Rani M, et al.: Association between buprenorphine dose and the urine "norbuprenorphine" to "creatinine" ratio: Revised. *Subst Abuse.* 2023; 17: 11782218231153748. DOI: 10.1177/11782218231153748.

15. Furo H, Schwartz DG, Sullivan RW, et al.: Buprenorphine dosage and urine quantitative buprenorphine, norbuprenorphine, and creatinine levels in an office-based opioid treatment program substance abuse: Research and treatment. *Subst Abuse.* 2021; 15: 1-9.

16. Krock K, Pesce A, Ritz D, et al.: Lower cutoff for LC-MS/MS urine drug testing indicates better patient compliance. *Pain Phys.* 2017; 7: E1107-E1113.

17. Krock K, Nickley J, Tran K, et al.: Correlation of fentanyl positive drug screens with other medications in patients from pain. *Rehabil Behav Prog Ann Clin Lab Sci.* 2020; 50(2): 55-60.

18. Pesce A, West C, West R, et al.: Reference intervals: A novel approach to detect drug abuse in a pain patient population. *J Opioid Manag.* 2010; 6: 341-350.

19. Pesce A, West C, West R, et al.: Determination of medication cutoff values in a pain patient population. *J Opioid Manag.* 2011; 7(2): 117-122.

20. West R, Pesce A, Crews B, et al.: Determination of illicit drug cutoff values in a pain patient population. *Clin Chim Acta.* 2011; 412: 1589-1593.

21. Nagpal G, Heiman H, Haymond S: Interpretation of urine drug screens metabolites and impurities. *JAMA Diagnostic Test Interpretation.* Available at *https://www.oregonpainguidance.org/wp-content/uploads/2018/02/Interpretation-of-UDS-JAMA-2017.pdf?x91687.* Accessed January 12, 2024.

22. Smiley S, Pesce A, Krock K, et al.: A comparison of urine and oral fluid drug testing. *J Clin Toxicol.* 2019; 9: 414. DOI: 10.4172/2161-0495.1000414.

23. Cua A, Krock K, Thomas R, et al.: Estimates of drug metabolism using drug excretion concentrations. *Ann Clin Lab Sci.* 2023; 53: 460-468.

24. Cua A, Krock K, Thomas R, et al.: Letter to Editor: Observations of deception in urine drug testing annals of clinical & laboratory science. *Ann Clin Lab Sci.* 2023; 53(4): 671-672.

25. Butrans Patch: Available at *https://www.drugs.com/pro/butrans-patch.html.* Accessed January 12, 2024. DOI: 10.1177/11782218211061749.