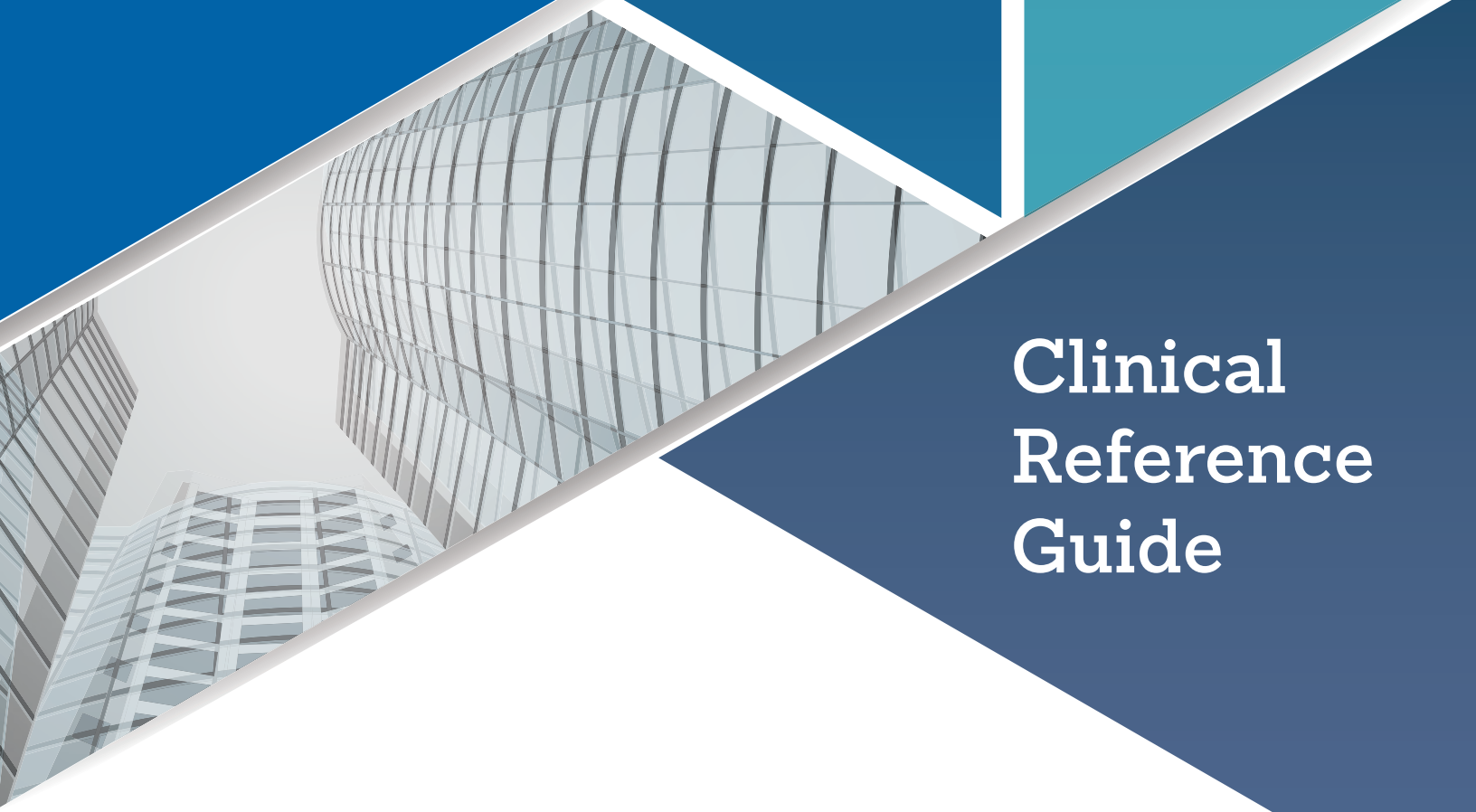
Helping Clinicians
Make Better Decisions

AEGIS® Sciences Corporation



Clinical Reference Guide

Point-of-Care Testing (POCT) – Interpreting Unexpected Results

Point-of-Care Testing (POCT) – Interpreting Unexpected Results

POCT is subject to limitations, and many drugs are excluded from this type of testing. Definitive testing methods such as gas chromatography/mass spectrometry (GC/MS) or liquid chromatography/tandem mass spectrometry (LC/MS/MS) rule out false positives and reduce the risk of false negatives.

Immunoassay is used in POCT programs in the outpatient and hospital settings and is employed as the first step of testing at many laboratories. Immunoassay technology has a number of features that make it popular in POCT situations; it is relatively simple to perform, fast, and economical. Unfortunately, drug discrimination and accuracy are significant limitations for immunoassay methods. There are different POCT devices, such as dipcards, cups, or tabletop analyzers, which may be targeted at individual drugs (e.g., cocaine) or classes of drugs (e.g., opiates). Most immunoassays used in POCT were not developed for use in clinical patient populations. Drug omissions and false negatives may result in an incomplete picture of patient drug and medication use. In addition, false positives are common, especially for drug classes such as opiates and amphetamines. Definitive testing of results is important to obtain prior to implementing changes to the patient care plan.

A. Clinical Implications of POCT

POCT may benefit pain management practices by dissuading new patients who are drug-seeking for addiction rather than pursuing adequate pain control. When faced with the prospect of a drug test or an immediate presumptive positive for an illicit drug such as cocaine, many illicit drug-using patients may elect to leave and pursue prescriptions for controlled substances elsewhere (presumably at a non-drug testing clinic). In addition, POCT results may be useful when evaluating a new patient and making the initial decision to write a prescription for a controlled substance. While any presumptive positive should be tested further by definitive testing, a presumptive positive for an illicit substance might lend support for providing only a short supply of medication(s) and setting up a return appointment for further evaluation once final definitive results are available. For these reasons, some clinics have found POCT useful.

However, the desire for an immediate answer may lead to hasty interpretations based on insufficient evidence. If practitioners begin to rely upon an immunoassay test and react to those results quickly, erroneous interpretation of false negative and false positive results may lead to significant patient harm.

B. POCT with Oral Fluid (OF)

The use of OF as an alternative matrix for the detection of drugs of abuse has increased over the last decade, leading to the desire for a rapid, simple, and reliable on-site OF testing device. Studies have evaluated multiple POCT devices for OF and drug detection in recovery centers as well as by police authorities conducting traffic-related stops in efforts to deter driving under the influence of drugs (DUID).[1-11] To date, there have not been POCT studies conducted to assess OF medication adherence testing in pain management populations. No POCT devices have the ability to detect all commonly prescribed or abused prescription drugs in OF. In studies evaluating OF POCT devices with the ability to test multiple drug classes in substance abuse recovery programs, none of the POCT devices were able to achieve good sensitivity across the board for every drug class included.[2,12] At this time, there is insufficient evidence to recommend POCT for OF.

C. Interpretation Considerations for Urine POCT

False Positives

Immunoassay technology, which is often used for POCT, presents the highest risk for false positives among all testing methods. Immunoassay is based on the principle of competitive binding of an antibody to a target analyte (or drug). If a drug is similar in structure to the target analyte, it may bind to the antibody and trigger a positive result. Additionally, some drugs with no clear structural similarity to the target analyte may still bind to the antibody. These cross-reacting compounds may result in false positives when testing by immunoassay.[13] When employed appropriately, GC/MS or LC/MS/MS

will identify each specific drug and metabolite, ruling out concerns for false positives that may be associated with immunoassay methods. Due to the extensive risk of cross-reactivity, positive drug tests by immunoassay should be called "presumptive positives."

The drugs which may cause false positives and the rates at which they do so will vary depending on the immunoassay characteristics adopted by the manufacturer. Not all cross-reacting compounds are well documented by manufacturers, and some choose

Table 8.1: *Cross-Reacting Compounds on Immunoassay*

IMMUNOASSAY TEST	POTENTIAL DRUGS CAUSING A FALSE POSITIVE OR UNEXPECTED POSITIVE RESULT		
Amphetamines[13,15-24]	Amantadine Aripiprazole Benzphetamine* Brompheniramine Bupropion Cathine Chloroquine Chlorpromazine Ciprofloxacin Clobenzorex Desipramine Dimethylamylamine Doxepin Ephedra Ephedrine Fenfluramine Fenproporex Fluorescein Fluoxetine	Ginkgo Isometheptene Isoxsuprine Labetalol l-Methamphetamine (OTC vapoinhaler)* m-Chlorophenylpiperazine (mCPP) MDA MDMA MDPV Mefanamic acid Mephentermine Metformin Methamphetamine* Methylphenidate Metronidazole Ofloxacin Phenmetrazine Phenothiazines Phentermine	Phenylephrine Phenylethylamine Phenylpropanolamine Promethazine Propranolol Propylhexedrine Pseudoephedrine Pyrovalerone Ranitidine Ritodrine Selegiline SodiumCyclamate Thioridazine Trancyclopromine Trazodone Trimethobenzamide Trimipramine Tyramine
Barbiturates[17,19,22]	NSAIDs (ibuprofen, naproxen)	Phenytoin	Tolmetin
Benzodiazepines[13,15,16,19,21,25]	Chlorpromazine Efavirenz Fenoprofen	Flurbiprofen Indomethacin Ketoprofen	Oxaprozin Sertraline Tolmetin
Buprenorphine[13,16,22,26]	Codeine Dihydrocodeine	Morphine Methadone	Tramadol
Cocaine[15,17,21]	Coca leaf tea* Ecgonine	Ecgonine methyl ester Topical anesthetics containing cocaine*	
Fentanyl[13,27,28]	Labetalol	Trazodone	Risperidone
Marijuana (THC)[13,15,16,19,21,29-31]	Acetylsalicylic acid Baby wash/soaps Cannabidiol Dronabinol*	Efavirenz Hemp-containing foods* NSAIDs (ibuprofen, naproxen) Proton pump inhibitors (pantoprazole)	Rifampin Tolmetin
Methadone[13,16,17,19,22]	Chlorpromazine Clomipramine Cyamemazine Diphenhydramine	Doxylamine Olanzapine Quetiapine	Tapentadol Thioridazine Verapamil
Opiates[13,15-17,22,32]	Dextromethorphan Diphenhydramine Doxylamine Heroin* Naloxone Pentazocine	Poppy seeds* Quinine (tonic water) Quinolone antibiotics (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin)	Ranitidine Rifampin Tolmetin Verapamil
Phencyclidine (PCP)[13,15,19,22,33]	Dextromethorphan Diphenhydramine Doxylamine Ibuprofen Imipramine	Ketamine Lamotrigine MDPV Meperidine Mesoridazine	Thioridazine Tramadol Venlafaxine, O-desmeth-yl-venlafaxine
Tricyclic Antidepressants[15,22,34]	Carbamazepine Cetirizine Cyclobenzaprine	Cyproheptadine Diphenhydramine Hydroxyzine	Promethazine Quetiapine

*These products either contain or metabolize to the target analyte, and are therefore a "true" positive result. The interpretation may not be easily obtained from the medical record.

not to make this information available. Many potentially cross-reacting substances are either unknown or commercially unavailable. Most immunoassay package inserts will address some, if not all, opportunities for cross-reactivity; however, the potential for false positives is likely to be underestimated.[14] Many widely-used prescription and over-the-counter drugs may trigger false positive results (see Table 8.1). Examples from literature of rates of positive immunoassay results that were negative upon definitive testing are provided in Table 8.2.

False Negatives

A true negative test result means that, at the time of collection, the concentration of a drug/metabolite fell below the test cutoff or threshold. Due to different rates of metabolism and excretion, and interpatient variability in a drug's period of detection, a true negative result may occur because the specimen was collected beyond the window of detection.

A false negative result occurs when a drug/metabolite was present in the specimen but was not detected by the testing method used. False negatives present a much greater threat in medication adherence testing than in a workplace urine drug testing setting, for which traditional drug testing protocols (and immunoassay tests) were developed. Appropriate test methods and techniques employed by laboratories may reduce the risk of false negatives, and it is important for practitioners to have a complete understanding of their laboratory's practices.

An exact rate of false negatives is difficult to predict, in part because they vary among different test methods and patient populations. The occurrence of false negatives with immunoassay test methods has been noted to vary significantly from lot to lot by the same manufacturer.[38] Examples of false negative rates with immunoassay testing that were reported in literature are given in Table 8.3. Immunoassay tests may result in false negative results for a variety of reasons, many of

Table 8.2: *Reported Rates of Postive Immunoassay Results Which Were Negative Upon Definitive Testing*

IMMUNOASSAY	MANCHIKANTI (2011)[35]	KIRSH (2015)[36]	JOHNSON-DAVIS (2016)[37]
Amphetamines	52.9%	21.4%	13.8%
Barbiturates	---	21.5%	2.5%
Benzodiazepines	---	11.4%	0.4%
Cocaine	0%	12.3%	0%
Marijuana	38.8%	21.3%	0.9%
MDMA/Methamphetamine	85.7%	99.5%	100%
Methadone	18.3%	45.3%	0%
Opiates	3.6%	22.4%	34%
Oxycodone	38.8%	41.3%	1.9%
PCP	---	100%	100%
TCAs	---	76.2%	---

Table 8.3: *Reported Rates of Positive Results by Definitive Testing Which Were Initially Negative by Immunoassay (False Negatives)*

DRUG CLASS	MIKEL (2009)[39]	PESCE (2010)[40]	MANCHIKANTI (2011)[35]	KIRSH (2015)[36]	Snyder (2017)[41]
Amphetamines	28.1%	9.3%	53%	43.9%	21.7%
Barbiturates	---	---	---	40%	---
Benzodiazepines	36.7%	22%	---	36.5%	34.6%
Cocaine	42.4%	50%	75%	40%	62.5%
Marijuana	38.2%	10.6%	9.1%	20.7%	---
Methadone	10.9%	6.1%	3.9%	27.9%	100%
Opiates	39.2%	1.9%	7.8%	29.9%	20.6%
Oxycodone	7.3%	---	24.6%	31.3%	7.5%
PCP	---	---	---	0%	---
TCAs	---	---	---	34.8%	---

which are described in more detail below.

• Incomplete Cross-Reactivity across a Drug Class

Immunoassays targeted at a drug class typically do not detect each drug within the class equally. In fact, many commonly prescribed drugs may not react at all upon immunoassay testing, obviously a significant concern for false negatives.

False negative results are common when opiate immunoassay methods are used to detect the most commonly prescribed opioids.[13] Most opiate immunoassays are developed to detect natural opiates such as codeine and morphine. However, these assays may not reliably detect semi-synthetic opioids, such as hydrocodone, oxycodone, and oxymorphone, even when these drugs are present at significant concentrations. An opiate false negative rate of up to 30% is described in one study of pain patients.[36] Another study demonstrated that 72.3% of negative opiate tests by immunoassay were positive upon GC/MS testing in patients prescribed hydrocodone or hydromorphone.[42]

Detection of certain benzodiazepines presents more difficulty than for others; providers should be familiar with their specific immunoassay and the corresponding cross-reactivity data. Many benzodiazepine immunoassays do not reliably detect alprazolam, clonazepam, and lorazepam, primarily due to lack of cross-reactivity with their metabolites.[13,15,16,43] In fact, a false negative rate of 50% was found for patients prescribed clonazepam and lorazepam in a study of 995 pain management patients.[43] A 2014 study illustrated benzodiazepine false negative rates as high as 53%.[44] Other studies have also echoed concerns for false negatives with benzodiazepines.[14,44] These concerns have led academic centers to advise against reliance on immunoassay tests to detect benzodiazepine use in clinical populations.[14,44,45] Direct-to-mass spectrometry methods are preferred for this drug class due to these significant immunoassay limitations.

• Lack of Cross-Reactivity with Metabolites

Most immunoassays are designed to react with a parent drug. Consequently, metabolites do not reliably result in a presumptive positive, and package inserts may exclude critical cross-reactivity information for major metabolites. This would cause limited concern if patients always excreted parent drug in urine, but practitioners should be aware that parent drugs may not always be present in urine, even with chronic use. Many drugs are largely excreted as metabolites; this is particularly true for opioids and benzodiazepines, which are extensively metabolized. In these cases, drug use may go undetected by an immunoassay test. A laboratory must test for drug metabolites when performing drug testing in clinical populations such as pain management and behavioral health. If clinically relevant metabolites are omitted, false negatives will inevitably result.

Most opioids are extensively metabolized by the cytochrome P450 (CYP450) system. Some metabolites are commercially available as separate pharmaceutical preparations. There are also opioid metabolites that are not available as drugs such as “normetabolites.” These are often important metabolite markers for their respective parent drugs. Examples include norbuprenorphine, norcodeine, norfentanyl, norhydrocodone, normeperidine, and noroxycodone. Normetabolite testing should be performed by definitive methods due to lack of cross-reactivity with immunoassays. Most immunoassay package inserts list poor cross-reactivity to normetabolites, and some do not even list normetabolite cross-reactivity.

Studies of drug excretion and urine prevalence consistently reveal that concentrations of normetabolites typically exceed parent drug concentrations.[46-50] Normetabolites may exhibit longer half-lives than parent compounds, accumulating with repeated use. They are also frequently the most persistent analyte during the terminal excretion phase. Drug-drug interactions with CYP3A4 inducers may also increase the probablity of finding normetabolites in absence of other drug markers.

• Drugs Not Included in Presumptive Testing

Many of the most frequently prescribed and abused drugs relevant to pain management are often omitted from onsite or POCT programs. For example, buprenorphine, fentanyl, meperidine, methadone, oxycodone, oxymorphone, tapentadol, and tramadol all require separate immunoassay tests apart from the

opiate panel. Other commonly abused prescription drugs, such as carisoprodol, may not be included in POCT.

• Presumptive Testing Thresholds Too High

Most immunoassay thresholds used in POCT were developed for workplace testing. These thresholds may not detect drugs in many instances of active use.[13,15,16,39] For example, most opiate urine immunoassay thresholds are 300 or 2,000 ng/mL, whereas a medication adherence threshold should be 50 or 100 ng/mL. Illicit drugs, such as marijuana and cocaine, typically have high thresholds on the most common POCT, and false negatives for illicit drugs are common with immunoassay methods when higher thresholds are used. Special attention should be paid to threshold selection for the clinical setting.[15]

• Sample Dilution, Adulteration, or Substitution

On-site tests are susceptible to sample adulteration and dilution. POCT may pose a problem if the patient provides a dilute sample, which effectively lowers the drug concentration to the extent the drug may fall below the testing threshold and result in a false negative. The importance of this must be recognized, as drinking large quantities of water to drive the drug concentration below thresholds is the most common method employed to beat a drug test. Patients may submit dilute specimens unintentionally as a natural consequence of increasing fluid intake in anticipation of providing a urine sample.[13,51] Specimen validity testing should be performed in order to identify unusually dilute urine specimens.

In addition, many of the immunoassay reagents used in tabletop analyzers are more susceptible to adulterants, which may be added to a specimen to mask the presence of illicit drugs.[16,52]

A substituted specimen may contain urine from another person or animal, synthetic urine, or some other fluid. Unless the donor procured urine from another drug-using friend, a substituted specimen is likely to result in a negative test.

• Result Interpretation Errors

On-site tests are subject to result interpretation errors. The results of POCT, particularly point-of-care cups, may be difficult to interpret. One study estimated that the results for approximately 4% of specimens could be misconstrued due to inconsistency in interpretation of a faint line on the particular point-of-care device.[43] A challenging aspect of interpretation is the fact that variation exists between devices made by different manufacturers.

Specific Drugs Not Identified

Immunoassays for opiates and benzodiazepines are limited to drug class, which may prove to be a disadvantage when a practitioner desires to identify the specific drug used. For example, a positive opiate immunoassay result does not differentiate between patients taking a prescribed opiate or illicit heroin. Assessing adherence with prescribed therapy can only be performed using mass spectrometry testing, which detects the specific drug or metabolite present.[13,15]

REFERENCES:

1. Strano-Rossie S, Castrignano E, Anziolloti L, et al. Evaluation of four oral fluid devices for on-site monitoring drugged driving in comparison with UHPLC-MS/ MS analysis. *Forensic Sci Int*. 2012;221(1-3):70-6.
2. Vanstechelman S, Isalberti C, Van der Linden T, Pil K, Legrand SA, Verstraete AG. Analytical evaluation of four on-site oral fluid drug testing devices. *J Anal Toxicol*. 2012;36(2):136-40.
3. Blencowe T, Pehrsson A, Lillsunde P, et al. An analytical evaluation of eight on-site oral fluid drug screening devices using laboratory confirmation results from oral fluid. *Forensic Sci Int*. 2011;208 (1-3):173-9.
4. Pehrsson A, Blencowe T, Vimpari K, Langel K, Engblom C, Lillsunde P. An evaluation of on-site oral fluid drug screening devices DrugWipe 5+ and Rapid STAT using oral fluid for confirmation analysis. *J Anal Toxicol*. 2011;35(4):211-8.
5. Wille SM, Samyn N, Ramirez-Fernández Mdel M, DeBoeck G. Evaluation of on-site oral fluid screening using Drugwipe-5(+), RapidSTAT and Drug Test 5000 for the detection of drugs of abuse in drivers. *Forensic Sci Int*. 2010;198(1-3):2-6.
6. Pehrsson A, Gunnar T, Engblom C, Seppä H, Jama A, Lillsunde P. Roadside oral fluid testing: comparison of the results of drugwipe 5 and drugwipe benzodiazepines on-site tests with laboratory confirmation results of oral fluid and whole blood. *Forensic Sci Int*. 2008;175(2-3):140-8.
7. Walsh JM, Flegel R, Crouch DJ, Cangianelli L, Baudys J. An evaluation of rapid point-of- collection oral fluid drug-testing devices. *J Anal Toxicol*. 2003;27(7):429-39.
8. Walsh JM, Crouch DJ, Danaceau JP, Cangianelli L, Liddicoat L, Adkins R. Evaluation of ten oral fluid point-of-collection drug-testing devices. *J Anal Toxicol*. 2007;31(1):44-54.
9. Crouch DJ, Walsh JM, Cangianelli L, Quintela O. Laboratory evaluation and field application of roadside oral fluid collectors and drug test devices. *Ther Drug Monit*. 2008;30(2):188-95.
10. Crouch DJ, Walsh JM, Flegel R, Cangianelli L, Baudys J, Atkins R. An evaluation of selected oral fluid point-of-collection drug-testing devices. *J Anal Toxicol*. 2005;29(4):244-8.

11. Scherer JN, Fiorentin TR, Borille BT, et al. Reliability of point-of-collection testing devices for drugs of abuse in oral fluid: A systematic review and meta-analysis. *J Pharm Biomed Anal*. 2017;143: 77-85.
12. Tang MHY, Ching CK, Poon S, et al. Evaluation of three rapid oral fluid test devices on the screening of multiple drugs of abuse including ketamine. *Forensic Sci Int*. 2018; 286:113-20.
13. Gourlay DL, Heit HA, Caplan YH. Urine drug testing in clinical practice: the art and science of patient care. 6th ed. Stamford, CT: PharmaCom Group, Inc.; 2015:1-32.
14. Melanson SEF, Ptolemy AS, Wasan AD. Optimizing urine drug testing for monitoring medication compliance in pain management. *Pain Med*. 2013;14:1813-20.
15. Moeller KE, Lee KC, Kissack JC. Urine drug screening: practical guide for clinicians. *Mayo Clin Proc*. 2008;83(1):66-76.
16. Reisfield GM, Goldberger BA, Bertholf RL. 'False-positive' and 'false-negative' test results in clinical urine drug testing. *Bioanalysis*. 2009;1(5):937-52.
17. Herring C, Muzyk AJ, Johnston C. Interferences with urine drug screens. *J Pharm Pract*. 2011;24(1):102-8.
18. Kaplan J, Shah P, Faley B, Siegel ME. Case reports of aripiprazole causing false-positive urine amphetamine drug screens in children. *Pediatrics*. 2015;136(6):e1625-8.
19. Brahm NC, Yeager LL, Fox MD, Farmer KC, Palmer TA. Commonly prescribed medications and potential false-positive urine drug screens. *Am J Health-Syst Pharm*. 2010;67:1344-50.
20. Marin SJ, Doyle K, Chang A, Concheiro-Guisan M, Huestis MA, Johnson-Davis KL. One hundred false-positive amphetamine specimens characterized by liquid chromatography time- of-flight mass spectrometry. *J Anal Toxicol*. 2016;40(1):37-42.
21. Smith ML. Immunoassay. In: Levine B, ed. *Principles of Forensic Toxicology*. 4th ed. Washington, D.C.: AACC Press;2013:149-69.
22. Saitman A, Park H-D, Fitzgerald RL. False-positive interferences of common urine drug screen immunoassays: a review. *J Anal Toxicol*. 2014;38(7):387-96.
23. Vorce S, Holler J, Cawrse B, Magluilo J. Dimethylamylamine: a drug causing positive immunoassay results for amphetamines. *J Anal Toxicol*. April 2011;35(3):183-7.
24. Pavletic AJ, Pao M. Popular dietary supplement causes false-positive drug screen for amphetamines. *Psychosomatics*. 2014;55(2):206-7.
25. Blank A, Hellstern V, Schuster D, et al. Efavirenz treatment and false-positive results in benzodiazepine screening tests. *Clin Infect Dis*. 2009;48(12):1787-9.
26. Shaikh S, Hull MJ, Bishop KA, et al. Effect of tramadol use on three point-of-care and one instrument-based immunoassays for urine buprenorphine. *J Anal Toxicol*. 2008;32(5):339-43.
27. Wang BT, Colby JM, Wu AH, Lynch KL. Cross-reactivity of acetylfentanyl and risperidone with a fentanyl immunoassay. *J Anal Toxicol*. 2014;38(9):672-5.
28. Ptolemy AS, Pecora N, Flood JG, Snyder ML, Melanson SE. Labetalol interference in a new fentanyl immunoassay. *Clin Chem*. 2012;58(10):S1.
29. Cotten SW, Duncan DL, Burch EA, Seashore CJ, Hammett-Stabler CA. Unexpected interference of baby wash products with a cannabinoid (THC) immunoassay. *Clin Biochem*. 2012;45(9):605-9.
30. Protonix [package insert]. Philadelphia, PA : Wyeth Pharmaceuticals Inc.;Feb 2017.
31. Epidiolex [package insert]. Carlsbad,CA : Greenwich Biosciences, Inc.; June 2018.
32. Straseki JA, Stolbach A, Clarke W. Opiate-positive immunoassay screen in a pediatric patient. *Clin Chem*. 2010;56(8):1220-5.
33. Macher AM, Penders TM. False-positive phencyclidine immunoassay results caused by 3,4-methylenedioxypyrovalerone (MDPV). *Drug Test Anal*. 2013;5:130-2.
34. Dasgupta A, Wells A, Datta P. False-positive serum tricyclic antidepressant concentrations using fluorescence polarization immunoassay due to the presence of hydroxyzine and cetirizine. *Ther Drug Monit*. 2007;29:134-9.
35. Manchikanti L, Malla Y, Wargo BW, Fellows B. Comparative evaluation of the accuracy of immunoassay with liquid chromatography tandem mass spectrometry (LC/MS/MS) of urine drug testing (UDT) opioids and illicit drugs in chronic pain patients. *Pain Physician*. 2011;14(2):175-87.
36. Kirsh KL, Heit HA, Huskey A, Strickland J, Egan K, Passik SD. Trends in drug use from urine drug testing of addiction treatment clients. *J Opioid Manage*. 2015;11(1):61-8.
37. Johnson-Davis KL, Sadler AJ, Genzen JR. A retrospective analysis of urine drugs of abuse immunoassay true positive rates at a national reference laboratory. *J Anal Toxicol*. 2016;40:97-107.
38. Hayden JA, Schmeling M, Hoofnagle AN. Lot-to-lot variations in a qualitative lateral-flow immunoassay for chronic pain drug monitoring. *Clin Chem*. 2014;60(6):896-7.
39. Mikel C, West R, Crews B, et al. LC-MS/MS extends the range of drug analysis in pain patients. *Ther Drug Monit*. 2009;31(6):746-8.
40. Pesce A, Rosenthal M, West R, et al. An evaluation of the diagnostic accuracy of liquid chromatography-tandem mass spectrometry versus immunoassay drug testing in pain patients. *Pain Physician*. 2010;13(3):273-81.
41. Snyder ML, Fantz CR, Melanson S. Immunoassay-based drug tests are inadequately sensitive for medication compliance monitoring in patients treated for chronic pain. *Pain Physician*. 2017;20:SE1-9.
42. Bertholf RL, Johannsen LM, Reisfield GM. Sensitivity of an opiate immunoassay for detecting hydrocodone and hydromorphone in urine from a clinical population: analysis of subthreshold results. *J Anal Toxicol*. 2015;39(1):24-8.
43. Mikel C, Pesce AJ, Rosenthal M, West C. Therapeutic monitoring of benzodiazepines in the management of pain: current limitations of point of care immunoassays suggest testing by mass spectrometry to assure accuracy and improve patient safety. *Clin Chim Acta*. 2012;413(15-16):1199-202.
44. Darragh A, Snyder ML, Ptolemy AS, Melanson S. KIMS, CEDIA, and HS- CEDIA immunoassays are inadequately sensitive for detection of benzodiazepines in urine from patients treated for chronic pain. *Pain Physician*. 2014;17(4):359-66.
45. Dixon RB, Floyd D, Dasgupta A. Limitations of EMIT benzodiazepine immunoassay for monitoring compliance of patients with benzodiazepine therapy even after hydrolyzing glucuronide metabolites in urine to increase cross-reactivity: comparison of immunoassay results with LC-MS/MS values. *Ther Drug Monit*. 2015;37:137-9.
46. Heltsley R, Zichterman A, Black DL, et al. Urine drug testing of chronic pain patients. II. Prevalence patterns of prescription opiates and metabolites. *J Anal Toxicol*. 2010;34(1):32-8.
47. DePriest A, Heltsley R, Black DL, et al. Urine drug testing of chronic pain patients. III. Normetabolites as biomarkers of synthetic opioid use. *J Anal Toxicol*. 2010;34(8):444-9.
48. Valtier S, Bebarta VS. Excretion profile of hydrocodone, hydromorphone and norhydrocodone in urine following single dose administration of hydrocodone to healthy volunteers. *J Anal Toxicol*. 2012;36:507-14.
49. Cone EJ, Heltsley R, Black DL, Mitchell JM, Lodico CP, Flegel RR. Prescription opioids. I. Metabolism and excretion patterns of oxycodone in urine following controlled single dose administration. *J Anal Toxicol*. 2013;37(5):255-64.
50. Cone EJ, Heltsley R, Black DL, Mitchell JM, Lodico CP, Flegel RR. Prescription opioids. II. Metabolism and excretion patterns of hydrocodone in urine following controlled single-dose administration. *J Anal Toxicol*. 2013;37(8):486-94.
51. Cone EJ, Caplan YH, Moser F, Robert T, Shelby MK, Black DL. Normalization of urinary drug concentrations with specific gravity and creatinine. *J Anal Toxicol*. 2009;33(1):1-7.
52. Warner A. Interference of common household chemicals in immunoassay methods for drugs of abuse. *Clin Chem*. 1989;35(4):648-1.