Prospective Evaluation

Utility of Oral Fluid in Compliance Monitoring of Opioid Medications

Till Conermann, MD, Ankur R. Gosalia, MD, Abraham Jack Kabazie, MD, Christina Moore, PhD, Kathy Miller, BA, Madalene Fetsch, MS, and Dwain Irvan, C (ASCP)CM

From: West Penn Allegheny Health System, Pittsburgh, PA

Address Correspondence:
Till Conermann, MD
West Penn Allegheny Health System
Anesthesiology and Pain Medicine
5124 Liberty Avenue
Pittsburgh, PA 15212
E-mail: tconerma@wpahs.org

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 02-16-2013
Revised manuscript received: 04-30-2013
Accepted for publication: 08-29-2013

Free full manuscript: www.painphysicianjournal.com

Background: Prescription drug abuse is the fastest growing drug problem in the United States, and the increase in unintentional drug overdose deaths has been driven by the increase in opioid analgesic use. Given the epidemic of non-medical prescription pain reliever use and the current medico-legal climate, it is increasingly important for the prescriber to monitor for medication compliance.

Objectives: The purpose of this IRB approved study is to compare the results of oral fluid (OF) and routine urinalysis for monitoring compliance in a single academic pain management program in an urban setting in order to evaluate the utility of OF analysis in compliance monitoring when prescribing opioid medications.

Study Design: Outcomes analysis of prospective, consecutive, paired comparison study with clinical implications.

Setting: Single academic interventional pain management center in the United States.

Methods: Paired OF and urine specimens were collected for each patient with signed informed consent, at the Institute for Pain Medicine, Western Pennsylvania Hospital, from patients who routinely donated urine on a random basis for compliance testing. A total of 153 paired specimens were analyzed. Demographic and prescription data were made available. Specimens were screened using immunoassay and presumptive positive findings were confirmed with liquid-chromatography and mass spectrometry. Although both matrices were tested for a wider range of medications, the data presented here are representative of analgesic opioids and benzodiazepine drug classes only.

Results: Following exclusion criteria, of the 132 remaining specimen pairs that were positive for opioids or benzodiazepines in at least one matrix, 101 pairs showed exact drug class matches (76.5%). In an additional 21 pairs, at least one drug class was positive in both matrices (15.9%), giving an overall agreement of 92.4%. Overall, 191 positive results were found in urine averaging 1.4 drugs per specimen; 176 positives were detected using OF for an average of 1.3 drugs per specimen.

Conclusions: In the setting of stable dosing of prescription opioids and/or concomitant illicit drug use, given comparable detection rates between urine and OF matrix qualitative results, the OF matrix for drug testing for compliance monitoring may serve as a useful and valid testing tool. The authors conclude that overall OF analysis produces comparable results to urine sample analysis with detection rates differing primarily due to differences in windows of detection for different drug classes.

Limitations: The limitations include the study was performed in a single academic center in an urban community. Also, there is a paucity of literature regarding windows of detection for OF analysis compared to urine.
IRB: APPROVED - Allegheny-Singer Research Institute West Penn Allegheny Heath System (ASRI-WPAHS) - IRB Study #FWA00015120

Key Words: Urine drug testing, oral fluid drug testing, saliva, opioids, drug abuse, compliance, chronic pain, diversion

Pain Physician 2014; 17:63-70

Opioid pain medications are often prescribed for the effective control of acute and chronic pain. However, with the legitimate use of prescription pain medications also comes the risk of misuse and diversion. The epidemic of opioid addiction and abuse has made it imperative for clinicians to monitor for medication compliance (1). Based on the available literature, monitoring aberrant behavior alone is inadequate and frequently results in clinicians underestimating aberrant drug-taking behavior. Taking advantage of the objectivity of urine drug testing in combination with monitoring for aberrant behavior has been recommended as the best available monitoring strategy. When prescribing chronic opioid therapy given the epidemic in the nonmedical use of opioids, routine urine drug testing has been recommended as part of an overall best practice program to include risk stratification, baseline and periodic urine drug testing, behavioral monitoring, and prescription monitoring programs. However given the associated costs and to avoid drug testing every patient at every visit and overburdening an economically strained health care system, rational risk-stratification approaches to routine urine drug testing have been recommended (2,3). Drug testing provides clinicians with objective evidence about their patients' appropriate use or potential misuse of their medications or evidence of recreational drug use. This information can be used to limit harm in patients and the community by helping detect medication misuse, polypharmacy, and diversion. Opioids such as oxycodone (e.g. OxyContin) and hydrocodone (e.g. Vicodin) are the most widely prescribed opioid pain-treatment medications and also are among the most abused drugs in the United States (4). Methadone (e.g. Methadose, Dolophine) has historically been used for treatment of opioid addiction, but is also used to treat moderate to severe pain, and recently has been considered the number one cause of accidental death due to opioid prescription medications in the United States (5). Studies have shown that in addition to opioids other controlled medications with abuse potential, such as benzodiazepines, are frequently prescribed in pain management therapies (6,7). Urinalysis drug testing is often used in pain management to monitor patient compliance, and is considered the gold standard by testing for the presence or absence of certain drugs to be evaluated with good specificity, sensitivity, ease of administration, cost, and longer windows of detection than serum (8). Oral fluid (OF) however has several advantages as a test matrix compared to urine since OF collections are typically observed, special facilities are not required, and OF is difficult to adulterate. Therefore, OF has been advocated as an alternative to urine for monitoring drug use and compliance in pain management as well as other testing areas (7,9). The purpose of this IRB approved study is to compare the results of OF and routine urinalysis for monitoring compliance in a single academic pain management program in an urban setting in order to evaluate the utility of OF analysis in compliance monitoring when prescribing opioid medications. The study was approved by the IRB (ASRI-WPAHS) IRB Study #FWA00015120.

Methods

Paired OF and urine specimens were collected for each patient with signed informed consent, at the Institute for Pain Medicine, from patients who routinely donated urine on a random basis for compliance testing. A total of 153 paired specimens were collected. OF specimens were collected with the Federal Drug Administration (FDA)-approved Quantisal™ device. The device consists of a cotton pad attached to a volume adequacy indicator that turns blue when one milliliter (+/- 10%) of OF has been collected. After the required volume is collected, the pad is placed into a transport tube containing buffer (3 mL) and sealed. The sealed-tube and OF specimen are then ready for shipment to the laboratory for analysis. Demographic and prescription data were made available. Urine specimens were tested using validated and certified Liquid Chromatography Triple Quadrupole Mass Spectrometry (LC/MS/MS) procedures at Forensic Laboratories, Denver, CO. The OF specimens were tested at Immunalysis Corporation, Pomona, CA. Both laboratories screened their respective specimens using immunoassay and confirmed presumptive positive findings with LC/MS/MS. The cut-offs used by each laboratory are described in Table 1 and Table 2 respectively. Although both matrices were tested for a wide range of medications, the data presented here are representative of analgesic opioids and benzodiazepine drug classes only. Outcomes analysis was subsequently performed by the authors of this prospective, consecutive, paired comparison study.

Results

During the specimen collection period (June 2011 – February 2012), 153 paired specimens were collected. Of the 153 specimens tested, 136 (88.8%) were positive for one or more treatment drugs in one matrix, or in both matrices (Table 3). All positive results were con-

Table 1. Oral fluid testing cut-off concentrations (Immunalysis Corporation). Screening: ELISA. Confirmation: LC/MS/MS.

Drug Class (Confirmed analytes)	OF Cut-off values (ng/mL)	
	Screening	Confirmation
Amphetamine/Methamphetamine (MDMA, MDA, MDEA, phentermine)	25	10
Barbiturates (phenobarbital, pentobarbital, secobarbital, butalbital)	50	50
Benzodiazepines (oxazepam, nordiazepam, bromazepam, estazolam, flurazepam, flunitrazepam, lorazepam, chlordiazepoxide, temazepam, diazepam, clonazepam, alprazolam, triazolam, midazolam, nitrazepam)	5	1
Buprenorphine	5	2
Cannabinoids (THC)	4	2
Carisoprodol (Soma)	50	50
Meprobamate	Not tested	Not tested
Cocaine (cocaine, cocaethylene, benzoylecgonine)	20	8
Dextromethorphan	50	20
EDDP	Not tested	Not tested
Ethyl alcohol	Not tested	Not tested
Fentanyl	1	0.5
Fluoxetine (Prozac)	50	10
Ketamine	10	10
Meperidine (Demerol)	50	25
Methadone	50	20
Methylphenidate (Ritalin)	10	10
Naloxone	Not tested	Not tested
Naltrexone	40	10
Opiates (6-AM, codeine, morphine, hydrocodone, hydromorphone)	20	10
Oxycodone (Percocet) (oxymorphone)	20	10
Phencyclidine	10	10
Propoxyphene (Darvon)	20	10
Sertraline (Zoloft)	50	10
Tapentadol	Not tested	Not tested
Tramadol (Ultram)	50	25
Tricyclic antidepressants (amitriptyline, nortriptyline, amoxapine, chlorpromazine, citalopram, clomipramine, cyclobenzaprine, desipramine, desmethyldoxepin, dothiepin, doxepin, imipramine, mianserine, mirtazipine, paroxetine, protriptyline, trazodone, trimipramine, venlafaxine)	25	10
Zolpidem (Ambien)	10	5

firmed with LC/MS/MS testing. There exists a potential for cross reactivity with OF and urine screening immunoassay testing. OF samples would have similar cross reactants to urine samples. All immunoassay results were confirmed with LC/MS/MS testing to assure against false positive tests caused by cross reactants. Three cases were excluded from the data because they were positive for one of the following drug classes that were not tested in both laboratories: anti-depressants, over the counter drugs, muscle relaxants, drugs of abuse, and/or 7-aminoclonazepam. One additional case was excluded because alprazolam and methadone were detected in the OF and there was insufficient volume to confirm the presence of methadone in the corresponding urine. Of the 132 remaining specimen pairs that were positive for opioids or benzodiazepines in at least one matrix, 101 pairs showed exact drug class matches (76.5%). In an additional 21 pairs, at least one drug class was positive in both matrices (15.9%), giving an overall agreement of 92.4%. Ten pairs had only one matrix

Table 2. *Urine Drug Testing Cut-off Concentrations . (Forensic Laboratories). Screening: EMIT*. Confirmation: LC/MS/MS**

Drug Class (Confirmed analytes)	**Urine Cut-off values (ng/mL*)**	
	Screening	**Confirmation**
Amphetamine/MDMA (MDMA, MDA, MDEA, amphetamine methamphetamine)	500	100
Barbiturates (Amobarbitol,butabarbital, phenobarbital, pentobarbital, secobarbital, butalbital)	200	200
Benzodiazepines (oxazepam, nordiazepam, estazolam, desalkylflurazepam, lorazepam, temazepam, alpha-Hydroxyalprazolam, alpha-Hydroxytriazolam, hydroxymidazolam) (7-Aminonitrazepam, 7-Aminoflunitrazepam, 7-Aminoclonazepam)	200	25
	Quantitative Test Only	75
Buprenorphine	Quantitative Test Only	5
Norbuprenorphine	Quantitative Test Only	25
Cannabinoids (Delta-9-THC-COOH)	25	5
Carisoprodol (Soma) (Carisoprodol) (Meprobamate)	100	100
	Not tested	250
	250	250
Cocaine (benzoylecgonine)	150	100
Dextromethorphan	Not tested	Not tested
Ethyl alcohol (Ethyl alcohol) (Ethyl glucuronide) (Ethyl sulfate)	0.05g/100mL(dehydro)	0.04g/100mL (GC-FID)
	Quantitative Test Only	500
	Quantitative Test Only	100
Fentanyl (Fentanyl) (Norfentanyl)	2	0.5
	Not tested	5
Ketamine	Not tested	Not tested
Meperidine (Demerol) (Meperidine, normeperidine)	200	100
EDDP (EDDP) (Methadone)	300	100
	Not tested	100
Methadone	Not tested(see above)	100
Methylphenidate (Ritalin)	Quantitative Test Only	100
Naloxone (Naloxone)	Quantitative Test Only	5
Naltrexone (Naltrexone, 6 Beta-naltrexol)	Quantitative Test Only	50
Opiates (codeine,norcodeine, dihydrocodeine, hydrocodone, norhydrocodone, morphine, hydromorphone)	300	50
6-Acetylmorphine (6-Acetylmorphine)	10	10
Oxycodone (Percocet) (oxycodone, noroxycodone, oxymorphone, noroxymorphone)	100	50
Phencyclidine (Phencyclidine)	25	25
Propoxyphene (Darvon) (Propoxyphene, norpropoxyphene)	300	100
SSRIs/SNRIs (sertraline, norsertraline, paroxetine, fluoxetine, norfluoxetine, citalopram, Desmethylcitalopram, Venlafaxine, O-desmethylvenlafaxine)	Quantitative Test Only	50
Tapentadol (Tapentadol, Desmethyltapentadol)	Quantitative Test Only	50
Tramadol (Ultram) (tramadol, desmethyltramadol)	100	100
Tricyclic antidepressants (amitriptyline, nortriptyline, desmethylclomipramine, clomipramine, desipramine, desmethyldoxepin, doxepin, imipramine, maprotiline, trimipramine)	Quantitative Test Only	50
Zolpidem (Ambien)	Not tested	Not tested

positive: 2 were OF positive and urine negative; 8 were urine positive and OF negative. Of the OF positive and urine negative paired samples, one OF was positive for both oxycodone and fentanyl; the other was positive for morphine. Of the 8 urine positive and OF negative paired samples, 3 were positive for buprenorphine at concentrations less than 25 ng/mL; 2 were positive for morphine; and one each was positive for oxycodone, hydrocodone, and hydromorphone. Overall, 191 positive results were found in urine averaging 1.4 drugs per specimen; 176 positives were detected using OF for an average of 1.3 drugs per specimen.

Also, there is a notable finding of 5 urine specimens positive for marijuana, yet negative for marijuana in their paired oral fluid samples.

Table 3. *Results of 153 paired specimen analyses.*

	Oral Fluid Positive	Oral Fluid Negative
Urine Positive	122	8
Urine Negative	2	17

Discussion

Historically urine has served as the specimen of choice for drug analysis and has been considered the most standardized for monitoring medication compliance in patients being prescribed opioids and other controlled medications. This is largely based on urine's windows of detection being up to 3 to 4 days for most opioid medications and being practical for detecting recent use in this detection window (10). Urine testing usually involves testing for metabolites and has advantages of relative ease of collection and less invasive collection technique when compared to blood. Disadvantages of urine drug testing include an inability to detect very recent use since it takes at least 6 to 8 hours for an oral medication's metabolites to start showing up in the urine (10). Other disadvantages include an inability to collect samples in anuric or oliguric patients or difficulty collecting in a timely fashion in patients that have recently voided. In addition, urine collection is commonly not observed in a clinical setting secondary to desire for patient privacy, which may allow for sample tampering.

With improvements in the collection and testing processes, OF is now very much a viable alternative matrix with possible applications in numerous testing environments including, but not limited to, drug screening, drug treatment programs, and in the setting of prescribed controlled substances to monitor for medication compliance (7,11). Reliability of testing results when comparing OF to urine specimens remains the focus of attention with differences in detection rates for different drug classes (7,10,12).

In this study, over 90% of samples were positive for at least one drug class in paired urine and OF specimens. In over 76% of samples an exact drug class match was attained. However, in this study there remains concern regarding the specimen pairs that were inconsistent. Eighty percent (8/10) of the inconsistencies were urine positive and OF negative, while 20% (2/10) were OF positive and urine negative. A multitude of factors are most likely involved in these discrepancies. The windows of detection for each matrix are determined by drug-class properties (e.g. lipid solubility, protein binding), patient metabolic rate (e.g. renal and hepatic function), chronicity and frequency of use, and specimen collection times during daily or weekly drug intake cycle (9). The route of medication administration and delivery may also play a significant role in the window of detection for OF versus urine sampling (9). Manufacturers may adjust their standardized immunoassay cut-off thresholds for each matrix. These threshold adjustments may potentially move patients from being negative to positive within low-level ranges, or vice versa. Depending on the testing cut off threshold, low-dose chronic use of certain opioids with high lipid solubility may show low levels in the urine but negative in OF such as transdermal fentanyl and/or buprenorphine (9,10,12). Lower detection rates of hydromorphone, oxymorphone, and buprenorphine are commonly noted during initiation or dosing changes of these agents, which may lead to discrepancies between urine and OF sampling (10,12). Of note, one patient within the study sample was detected positive for fentanyl in OF but negative in urine which the authors believe may be due to possible recent oral dosing of fentanyl such as with Fentora or Actiq use or possible recent misuse of the transdermal application via oral route. In this patient the medication and its metabolites have not yet had time to be excreted into the urine, resulting in a negative urine analysis for fentanyl. Nearly all of the other discrepancies are likely the direct result of windows of detection and/or cutoff thresholds.

Conversely, in a urine positive patient where the OF analysis was negative for an opioid, this is likely attributable to no recent use within one day and the lack of a detectable saliva level. Recall that saliva levels correlate closely with blood levels. This patient's urine would be expected to be positive for opioid metabolites if taken within the last 3 to 4 days.

OF testing offers several major advantages over

Table 4. *Windows of detection in urine and oral fluid for commonly prescribed opioids following single dose (14,15).*

DRUG	Detection time in Oral Fluid	Detection time in Urine
Morphine	24 hours	36 – 72 hours
Codeine	7 – 21 hours	24 – 48 hours
Oxycodone	Not Available	12 – 48 hours
Hydrocodone	7 – 21 hours	12 – 36 hours
Oxymorphone	Not Available	12 – 36 hours
Hydromorphone	6 hours	12 – 96 hours
Fentanyl (transdermal)	Not Available	Not Available
Fentanyl (transbuccal)	Not Available	Not Available
Buprenorphine (sublingual)	Not Available	Not Available
Methadone	24 hours	12 – 96 hours

urine sampling. The integrity of the specimen is considered by many to be more reliable since collection is easily observed without loss of privacy. Specimen manipulation (e.g. urine exchange, urine tampering with adulterants) is less likely with OF when observation of specimen collection is unhindered. No special facilities are required for OF sampling and it can easily be performed in the exam room. Another advantage of the OF matrix is levels do approximate blood levels of opioid and benzodiazepine medications, and therefore may more accurately identify recent intake as seen in blood and saliva before being detectable in urine (9,12,13). Urine levels of metabolites may fluctuate significantly secondary to multiple factors including hydration, metabolism, and time following last dose. Urine concentrations are not considered reliable in certain settings since they do not correlate accurately with blood levels. In this cohort of cases, OF also seems more reliable in detecting 6-acetylmorphine (6-AM), a metabolite of heroin. OF levels are generally similar to blood concentrations following intravenous abuse, but may be substantially higher than blood following the smoking of heroin due to possible residual drug deposited in the oral mucosa (14) (Table 4).

Several concerns remain regarding certain aspects of OF testing and its application in daily clinical practice. Although both urine and OF analysis require mass spectroscopy confirmation following positive-screen analysis, laboratory cost of testing of saliva in the past was higher when compared to urine analysis due to the increased level of sensitivity required in the instrumentation of OF analysis. This has largely been offset with technological advancements. Over the past 2 years the cost of OF analysis has seen consistent quarterly decreases and the cost difference between OF and urine analysis is predicted to continue to decline. Despite the usefulness of urine drug testing in ensuring compliance by patients and in monitoring the use of non-prescribed or illicit substances in the population receiving opioid therapy for chronic pain, there have been concerns raised that it has been over-used, misused, and abused due to financial incentives, and due to the influence of medical licensure boards, the Drug Enforcement Agency (DEA), and other governmental agencies (8). As with any new test, depending on how it is used, marketed, and billed for, OF testing may be subject to similar concerns as well. The recommended and rational risk-stratification approaches for routine urine drug testing (2) should also be followed for OF testing to help facilitate appropriate utilization.

Result turnaround time has also been a concern regarding OF analysis, but recently liquid chromatography-tandem mass spectroscopy has been utilized on OF with a run time of as little as 14 minutes with possible application for rapid screening protocols (15). Many laboratories now publish matching turnaround times for urine and OF samples. Also, a potential concern in the setting of xerostomia is the increased time required for production of necessary saliva for accurate testing which can occur during specimen collection. However difficulties and delays in obtaining a sample also occur with urine sample collection in patients who are dehydrated, who have recently voided, or who have renal insufficiency or failure. Although the window of detection within OF is earlier for most agents tested, the window of detection for nearly all opioids is shorter when compared to urine, which may be of concern in the setting of intermittent dosing or low-level dosing regimens (12). Primary exceptions to agreement between urine and OF are relative lower rates of detection for hydromorphone, and oxymorphone in OF (12). Also of note in this study, OF proved to be a poor detector of marijuana use when compared to their paired urine specimens.

Route of administration of cannabis influences blood concentrations and time-to-peak effects. THC appears rapidly in plasma if inhaled, whereas oral ingestion delays time-to-peak effect and generally produces lower blood concentrations. THC is very lipophilic which results in rapid tissue uptake with concomitant decreases in plasma levels. THC is released slowly from tissue resulting in a prolonged half-life of THC and its metabolites. THC metabolites are found in OF in very

low concentrations, are difficult to detect, and have a short window of detection (13,14). Immediately after smoking, very high levels (typically > 200 ng/mL) may be found in OF and serum, but a rapid decline is noted likely due to tissue uptake. The available evidence seems to indicate that THC is present in oral fluid primarily as a result of direct deposition in the oral cavity instead of from transfer from blood into the saliva as with most other ingested drugs of abuse (13,14). Passive inhalation did not produce positive OF tests. Testing for 11-nor-delta-9-tetrahydrocannabivarin-9-carboxylic acid (THCV-COOH), an oxidative metabolite of delta-9-tetrahydrocannabivarin found naturally in cannabis compounds (i.e. Sativex), but not in synthetic THC (i.e. Marinol), has been suggested as a possible tool in helping to differentiate illicit cannabis use from synthetic THC in both urine and saliva samples (13,14).

This study provides evidence that OF and urine specimens have comparable detection rates between matrix qualitative results. As is the case when evaluating results of urine drug testing, the results of OF testing need to be interpreted in the context of the individual patient. Specifically, focus should be placed on the patient's opioid regimen (sustained-release versus short-acting), the timing of their last dose, dose frequency, and potential inter-individual variability in metabolism. Any observed differences in qualitative measurements in urine and OF can be explained in large part by differences in the windows of detection for specific drugs and their metabolites (7,9, 10,12,13,14). In the setting of stable dosing of prescription opioids and/or concomitant illicit drug use, given comparable detection rates between urine and OF matrix qualitative results, the OF matrix for drug testing for compliance monitoring can serve as a useful and valid testing tool. The authors conclude that overall OF analysis produces comparable results to urine sample analysis with detection rates differing primarily due to differences in windows of detection for different drug classes.

Conclusions

Prescription drug abuse is the fastest growing drug problem in the United States, and the increase in unintentional drug overdose deaths has been driven by the increase in opioid analgesic use (4). Given the epidemic of non-medical prescription pain reliever use and the current medico-legal climate, it is increasingly important for the prescriber to monitor for medication compliance. Validity drug testing has become a standard of care by helping to detect and deter the use of unauthorized medications, medication misuse, and/or illicit drug use. Drug testing has the potential to minimize harm by decreasing the risk of toxicity related to poly-pharmacy by early detection and modifying treatment plans, as well as by detecting diversion. Urine drug analysis with validity testing remains the gold standard for compliance monitoring in pain patients. In this study, over 90% of the paired samples were positive for at least one drug class in paired urine and OF specimens. Over 75% of the paired samples showed exact drug class matches. OF and urine provided comparable detection rates between matrix qualitative results. OF offered several collection advantages: No special facilities were required, patient privacy was maintained even though the process was totally observed, and the integrity of the specimens was ensured. This project confirmed OF as a reasonable alternative matrix for the detection of prescription medications and its value as a specimen for monitoring patient compliance.

References

1. Dunn K, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Korff MV. Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann of Int Med* 2010; 152:85-92.
2. Owen GT, Burton AW, Schade CM, Passik S. Urine drug testing: Current recommendations and best practices. *Pain Physician* 2012; 15:ES119-ES133.
3. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel.Opioid treatment guidelines: Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J of Pain* 2009; 10:113-130.
4. Paulozzi L, Baldwin G, Franklin G, Kerlikowske RG, Jones CM, Ghiya N, Popovic T. CDC grand rounds. Prescription drug overdoses – a US epidemic. *CDC MMWR* 2012; 61:10-13.
5. Paulozzi LJ, Mack KA, Jones CM. CDC vital signs. Risk for overdose from methadone used for pain relief – United States 1999 – 2010. *CDC MMMR* 2012; 61:493-497.
6. Cone EJ, Caplan YH, Black DL, Robert T,

Moser F. Urine drug testing of chronic pain patient: Licit and illicit drug patterns. *J Anal Toxicol* 2008; 32:530-543.

7. Heltsley R, DePriest A, Black DL, Robert T, Marshall L, Meadors VM, Caplan YH, Cone EJ. Oral fluid drug testing of chronic pain patients. I. Positive prevalence rates of licit and illicit drugs. *J Anal Toxicol* 2011; 35:529-540.
8. Christo PJ, Manchikanti L, Ruan X, Bottros M, Hansen H, Solanki DR, Jordan AE, Colson J. Urine drug testing in chronic pain. Comprehensive review. *Pain Physician* 2011; 14:123-143.
9. Verstraete AG. Detection times of drugs of abuse in blood, urine, and oral fluid. *Ther Drug Monit* 2004; 26:200-205.
10. Vindenes V, Yttredal B, Oiestad EL, Waal H, Bernard JP, Morland JG, Christophersen AS. Oral fluid is a viable alternative for monitoring drug abuse: Detection of drugs in oral fluid by liquid chromatography-tandem mass spectrometry and comparison to the results from urine samples from patients treated with methadone or buprenorphine. *J Anal Toxicol* 2011; 35:32-39.
11. Oiestad EL, Johansen U, Christophersen AS. Drug screening of preserved oral fluid by liquid-chromatography tandem mass spectrometry. *Clin Chem* 2007; 53:300-309.
12. Heltsley R, DePriest A, Black DL, Crouch DJ, Robert T, Marshall L, Meadors VM, Caplan YH, Cone EJ. Oral fluid drug testing of chronic pain patients. II. Comparison of paired oral fluid and urine specimens. *J Anal Toxicol* 2012; 36:75-80.
13. Cone EJ. Saliva testing for drugs of abuse. *Ann NY Acad Sci* 1993; 20:91-127.
14. Cone EJ, Huestis MA. Interpretation of oral fluid tests for drugs of abuse. *Ann N Y Acad Sci* 2007; 1098:51-103.
15. Meoller KE, Lee KC, Kissack JC. Urine drug screening: Practical guide for clinicians. *Mayo Clin Proc* 2008; 83:66-76.