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Comprehensive Review

# Urine Drug Testing In Chronic Pain

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Therapeutic use, overuse, abuse, and diversion of controlled substances in managing chronic non-cancer pain continue to be an issue for physicians and patients. The challenge is to eliminate or significantly curtail abuse of controlled prescription drugs while still assuring the proper treatment of those patients. Some physicians are apprehensive regarding the use of chronic opioid therapy in chronic non-cancer pain due to a perceived lack of proven evidence, the misuse of opioids, tolerance, dependence, and hyperalgesia. However, others have criticized the underuse of opioids, resulting in the undertreatment of pain. It has been the convention that federal, state, and local governments; professional associations; as well as pharmaceutical companies, physicians, accrediting bodies, medical licensure boards, and the public all share responsibility for preventing abuse of controlled prescription drugs.

To overcome the critical challenge of eliminating or significantly curtailing abuse of controlled prescription drugs and at the same time assuring the appropriate treatment for those patients who can be helped by these medications, it is crucial to practice adherence or compliance monitoring of opioid therapy.

Compliance monitoring has been shown to be crucial in delivering proper opioid therapy and preserving this therapy for the future. Urine drug testing (UDT) is considered one of the mainstays of adherence monitoring in conjunction with prescription monitoring programs and other screening tools, however, UDT is associated with multiple limitations secondary to potential pitfalls related to drug metabolism, reliability of the tests, and the knowledge of the pain physician.

UDT is a widely available and familiar method for monitoring opioid use in chronic pain patients. UDT can provide tools for tracking patient compliance and expose possible drug misuse and abuse. UDT is one of the major tools of adherence monitoring in the assessment of the patient's predisposition to, and patterns of, drug misuse/abuse – a vital first step towards establishing and maintaining the safe and effective use of opioid analgesics in the treatment of chronic pain.

This comprehensive review provides the role of UDT in monitoring chronic opioid therapy along with reliability and accuracy, appropriate use, overuse, misuse, and abuse.

**Key words:** Controlled substances, opioids, benzodiazepines, illicit drugs, abuse, diversion, prescription monitoring programs, adherence monitoring, compliance monitoring, urine drug testing, immunoassay, chromatography, false-positives, false-negatives.

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The use of prescription opioids has increased over the last 10 years as an accepted method for treating chronic nonmalignant pain (1-14). Concurrently, there has been a greater incidence of prescription drug abuse as demonstrated by epidemiologic, emergency room, and treatment admission data (1-8,14-47). The challenge of using opioid analgesia therapy lies in balancing 2 important public health concerns: responding to the need of relieving chronic pain and preventing the overuse or abuse of opioid medications (1-5,10-14,48-61). Physicians have long been apprehensive regarding the use of this therapy due to a perceived lack of proven evidence (1,5,10-14,56-66), the misuse of opioids (e.g., addiction, diversion, abuse), tolerance, cognitive effects, dependence, and hyperalgesia, all of which have contributed to the alleged under utilization of opioid therapy as perceived by some proponents of opioid therapy (1-3,5,8-14,52,56-74). Clinicians caring for patients with chronic pain often struggle to provide adequate pain control while avoiding the risk of substance abuse (1,3-5,14,48-51,53). Reasons to test patients for appropriate use of opioids may be summarized as the following 10 P's:

1) Protecting the patient
2) Protecting the practitioner
3) Protecting the pain therapy plan
4) Protecting the community
5) Protecting society
6) Promoting cost-effectiveness
7) Protecting resources
8) Practicing safe and effective medicine
9) Practicing and fulfilling ethics in medical practice
10) Preserving access to therapy.

In order to achieve this, federal, state, and local governments; professional associations, as well as pharmaceutical companies, physicians, accrediting bodies, medical licensure boards, and the public must all share responsibility for preventing improper use, misuse, and abuse of controlled prescription drugs (1,3,4,6,14). However, the critical challenge remains to eliminate or significantly curtail abuse of controlled prescription drugs while still assuring the appropriate treatment of those patients who can be helped by these medications, and avoid labels such as opiophobia and undertreatment of pain (1,5,14,67,68,71-75). To achieve these goals, it is crucial to allow accurate clinical and administrative, including legal and governmental, assessment of the true nature and scope of prescription and illicit drug use and abuse; provide physicians' insight to patients' patterns of drug use and compliance so as to direct the type and conduct of treatment that can and should be provided; and finally, ensure the safe, ethical, and legal sound practice of medicine while maintaining patient access to these therapies. Adherence monitoring has been shown to be a useful approach to acquiring information from biological, psychological, and social domains that can assist in identifying and/or predicting patterns of drug use, compliance, misuse, and abuse (1,13,14,16,76).

## 1.0 Chronic Non-Cancer Pain

Chronic non-cancer pain has been defined by the American Society of Interventional Pain Physicians (ASIPP) as, "pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal, that is associated with chronic pathologic processes that cause continuous or intermittent pain for months or years, that may continue in the presence or absence of demonstrable pathologies; may not be amenable to routine pain control methods; and healing may never occur (75,77)." Chronic persistent pain is associated with significant impairment of physical and psychological health, and performance of social responsibilities, including work and family life (76-84). Recent studies have shown significant increases in prevalence and associated disability of chronic pain (82,83). In fact, a study performed in the United States (83) showed an annual increase of 11.6% for low back pain.

### 1.1 Opioids in Chronic Non-Cancer Pain

Opioids have been used for thousands of years to treat pain, and continue to be one of the most commonly prescribed medications for chronic pain. Even though opioids have been controlled in the United States with regulations and restrictions, opioid utilization has been increasing at an unprecedented pace (1-10). Manchikanti et al (1), in an evaluation of opioid usage over a period of 10 years, showed an overall increase of 149% in retail sales of opioids from 1997 to 2007 in the United States, with an increase of 1,293% for methadone, 866% for oxycodone, and 525% for fentanyl. Similarly, the increase in therapeutic opioid use in the United States in milligrams per person from 1997 to 2007 increased 402% overall, with the highest increase in methadone of 1,124% mg/person and oxycodone of 899% mg/person.

Despite the extensive use of opioids, the evidence of its effectiveness, not only on pain relief, but also on

functional status and quality of life indicators, has been limited (5,10-14,56-66,85). In fact, it has been shown that opioid use might go against other important principles of chronic pain management, aiming at increased self-efficacy, reduced reliance on the health care system, reinforcement of pain behavior, and passivity and loss of autonomy by externalization of the locus of control (85). In an epidemiologic study, Eriksen et al (61) showed that in Denmark, the results were worse pain, higher health care utilization, and lower activity levels in opioid-treated patients compared with a matched cohort of chronic pain patients not using opioids.

### 1.2 Opioid Abuse in Chronic Pain

Abuse of opioids in chronic non-cancer pain is considered one of the urgent issues in modern medicine, with over 90% of patients presenting to interventional pain management settings already on opioid therapy. Drug abuse has been estimated to be in the range from 18% to 41% of patients receiving opioids for chronic pain (15-23,56,85-96).

### 1.3 Illicit Drug Use in Chronic Pain

In addition to opioid abuse, illicit drug use in patients in chronic pain management settings without controlled substance use was found in 14% to 16% of patients and illicit drug use in patients with controlled substance use was present in 34% of the patients (17,89-91). Adherence monitoring has been shown to decrease controlled substance abuse and illicit drug use (15,16).

### 1.4 Drug Diversion in Chronic Pain

Prescription drug diversion, defined as the unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace, has been a topic of widespread commentary and is of interest to regulators and providers (97). The abuse of many different prescription drugs has been escalating since the early to mid 1990s (1-14,97-100). While diversion can occur in many ways, including illegal sale of prescriptions by physicians, patients, and pharmacies, doctor shopping, forgery, robbery, and theft, it has been shown that the majority of the drugs come from a single physician's prescription and that family members share it (47).

### 1.5 Terminology of Abuse

Much confusion has resulted from the different uses of the terms "addiction," "physical dependence," and "tolerance" among clinicians and even medical organizations. For example, addiction is characterized by the following: maladaptive behavior due to the use of drugs, loss of control over drug use, and preoccupation with obtaining opioids despite having adequate pain control (101). Physical dependence refers to a state of adaptation manifested by drug class-specific withdrawal syndrome possibly produced by abrupt cessation of the drug, rapid dose reduction, decreasing blood levels of the drug, and/or administration of an antagonist (101). Tolerance is indicated by the need for increasing doses of a medication to achieve the initial effects of the drug.

Opioid abuse refers to the willful misuse of opioids and arguably includes drug diversion, since selling the drug rather than taking it is willful misuse (1,14,48,49,51). A 2008 review found that a small percentage of patients suffering chronic pain who are prescribed opioids will develop addiction or abuse to the drug (3.27%) and a larger percentage will demonstrate some aberrant drug-related behaviors and illicit drug use (11.5%) (70). An earlier study reported 23% of chronic pain patients prescribed opioids will become addicted (102) and other investigators state that drug overuse, misuse, or abuse might have a prevalence of above 40% (1-9,15-23,51-55,59,85-91,102-108).

## 2.0 Compliance for Proper Use of Opioids

Compliance monitoring for proper use of opioids is crucial in delivering proper opioid therapy and preserving this therapy for the future. Opioid therapy may be provided individually as monotherapy or it may be provided in conjunction with other therapeutic modalities including interventional techniques, rehabilitation therapy, and surgical interventions (75,109-135). The latter is utilized more often than the first. For the proper use of opioids, one should consider providing multidisciplinary therapies or at least prescribe them in conjunction with other modalities as a supplemental therapy based on evidence. In fact, multiple interventional therapies have been illustrated to be beneficial in managing chronic persistent non-cancer pain; low dose opioids improved functional status, even though there had not been a significant change in opioid intake (75,109-135). Similar to escalating opioid therapy, interventional techniques, surgical interventions, and all other modalities of treatments also have been criticized for overuse, misuse, and abuse (67,68,136-149).

### 2.1 Screening for Opioid Abuse

Screening for opioid misuse and abuse is an exercise to strengthen the patient-physician relationship.

This should not be confrontational and the patient has to understand that this is like any other laboratory test. Thus, a physician would respond to adherence monitoring or screening for opioid abuse similar to how one would respond to an abnormal liver function test or anemia. Further, several investigators have described multiple screening instruments in detecting opioid abuse or misuse in chronic pain patients (5,11,13,76,150-152). However, there is no widely used or reliable screening instrument available in current practice.

While routine urine drug testing (UDT) has become standard in the addiction treatment setting, it has not been universal in chronic pain management centers or with internists or family practitioners who treat a smaller number of chronic pain patients. In fact, in a systematic review of treatment agreements and UDT to reduce opioid misuse in patients with chronic pain (153), the evidence was relatively weak in supporting the effectiveness of opioid treatment agreements and UDT in reducing opioid misuse by patients with chronic pain. It was concluded that family medicine physicians who order UDT to monitor their patients on chronic opioid therapy are not proficient in their interpretation (154). Another study evaluating drug testing of adolescents in ambulatory medicine (155) concluded that primary care physicians do not always use proper urine sample collection and validation procedures, and they are not aware of important limitations of drug testing. In a survey conducted in 2008 by the Biomedical Research and Education Foundation (BREF), based on a questionnaire distributed to 99 attendees (51), it was concluded that most urine testing was motivated by a desire to detect undisclosed substances than to evaluate appropriate opioid use. However, some responders never urine-tested their opioid patients, and about two-thirds of the respondents had no formal training in urine testing of patients on opioid therapy (51). The authors concluded that urine testing was not used consistently. In an editorial (156) accompanying the previous study (51), Bair and Krebs (156) questioned why UDT is not used more often in practice. Even though there is no evidence-based literature for utilization of UDT, they recommended clinician training programs, continuing education, recognition of best practices, and ready access to expert consultation are necessary, but not likely sufficient to promote greater use of this potentially valuable tool. Ultimately, they contend that to improve the safe and effective use of opioids, the health care system and individual practices will need to be redesigned to support routine UDT in conjunction with other opioid monitoring strategies.

## 3.0 Urine Drug Testing

There are a variety of biological specimens used in performing laboratory drug testing (e.g., urine, blood, sweat, saliva, hair, and nails). Each provides differing levels of specificity, sensitivity, and accuracy. No single instrument or assessment method has universal predictive utility because there could be multiple reasons and factors involved in drug abuse and/or misuse. However, UDT is regarded as the gold standard. This is primarily because urinary tests allow for the presence or absence of certain drugs to be evaluated with good specificity, sensitivity, ease of administration, and cost (49). Urine drug concentrations and metabolites also tend to be high in urine, allowing longer detection times than serum concentrations (54). However, debate continues regarding the clinical value of UDT, partly because most current methods are designed for, or adapted from, forensic or occupational deterrent-based testing for illicit drug use and are not entirely optimal for applications in the chronic pain management setting (49). Yet, with appropriate consideration of the caveats against misinterpretation (arising from limits of specificity, and/or false-positive or false-negative screens), UDT can be a useful tool to aid in both the ability to evaluate patients' compliance with prescribed regimens of controlled substances, and to diagnose the misuse or abuse of prescribed drugs or use of illicit agents. However, UDT has been used, misused, and abused due to financial incentives, and the influence of medical licensure boards, the Drug Enforcement Agency (DEA), and other governmental agencies (49,68,69,110,111,157,158). UDT is most commonly used for 2 purposes: ensuring compliance by patients who are using the prescribed opioid(s), and monitoring the use of non-prescribed or illicit substances in the population receiving opioid therapy for chronic pain (87).

### 3.1 Historical Aspects

The history of UDT dates back to a 1790 statute authorizing that every soldier be given a daily ration of a quarter pint of rum, whiskey, or brandy (159). Subsequently, over the next 200 years or so, the ill effects of alcohol and drugs in the workplace were recognized. Consequently, in the early 1980s, the U.S. military introduced a "zero tolerance" random drug testing policy after an explosion aboard the USS Nimitz in which postmortem examinations showed that half of the crew members who were killed tested positive for marijuana. Over the next 8 years, illicit drug use in the military dropped from 30% to 5% (160). Further,

in 1986, President Reagan issued an Executive Order on the Drug Free Federal Workplace, which mandated each executive agency to establish a program to test for drug use by federal employees in "sensitive" positions. This program mandated drug testing following accidents in those for whom there was a reasonable suspicion of use, and for new job applicants (161). The Department of Transportation also enacted a similar program in 1987 (159). Since then, UDT has become a common practice in the American workplace.

## 3.2 Limitations of Application of Urine Drug Testing

Nafziger and Bertino (53) described various scientific principles of pain medicine pharmacology that affect UDT findings and are important to consider. These include sources of variability in pharmacokinetics, pharmacodynamics (pharmacologic effects), pharmacogenetics (the effect of genetics and the environment on pharmacokinetics and pharmacodynamics), and also issues relating to the collection, handling, and assay methodologies for urine. In addition, it is essential to avoid adulteration and subversion of UDT, and to ensure validity. As important a tool as UDT is in the treatment of chronic pain, it nevertheless remains only one of many tools.

Methods for accurate UDT have been available for several decades, and such methods are useful in assessing and identifying substance use. Despite widespread adoption of UDT in multiple settings, studies have shown that medical students and residents receive inadequate training in these techniques, and practitioners are not very familiar with applications and implications of UDT (51,153-155).

### *3.2.1 Variables Affecting Results of Urine Testing*

Multiple variables affecting the results of urine testing include cutoff selection; pharmacokinetics, pharmacodynamics, and pharmacogenetics; laboratory technology used in the urine drug test; and subversion and adulteration of the urine specimen.

#### 3.2.1.1 Cutoff Selection

One variable influencing drug detection is the cutoff threshold. In other words, any sample having a drug concentration equal to or above a specified level is considered a "positive result." This threshold might vary from context to context as well as from screen to conformation test. These concentrations are illustrated in Table 1. Screening cutoff concentrations and confirmation cutoff concentrations are variable for certain drugs such as amphetamines, cocaine, marijuana, and methamphetamine. Further, there might also be differences between confirmation cutoff concentrations for regulated and non-regulated testing. A lower cutoff results in a longer detection time, even though it also affects

Table 1. *Urine drug testing: Typical screening and confirmation cut-off concentrations and detection times for drugs of abuse.*

| Drug | Screening cut-off concentrations ng/mL urine | Confirmation cut-off concentrations ng/mL (non-regulated) | Confirmation cut-off concentrations ng/mL (federally regulated) | Urine detection time |
|---|---|---|---|---|
| Opioids | | | | |
| Morphine | 300 | 50 | 2,000 | 3-4 days |
| Codeine | 300 | 50 | 2,000; 300 | 1-3 days |
| Hydrocodone | 300 | 50 | 2,000 | 1-2 days |
| Oxycodone | 100 | 50 | 2,000 | 1-3 days |
| Methadone | 300 | 100 | 2,000 | 2-4 days |
| Benzodiazepines | 200 | 20-50 | NA | Up to 30 days |
| Cocaine | 300 | 50 | 150 | 1-3 days |
| Marijuana | 50 | 15 | 15 | 1-3 days for casual use; up to 30 days for chronic use |
| Amphetamine | 1,000 | 100 | 500 | 2-4 days |
| Methamphetamine | 1,000 | 100 | 500 | 2-4 days |
| Heroin* | 10 | 10 | NA | 1-3 days |
| Phencyclidine | 25 | 10 | 25 | 2-7 days for casual use; up to 30 days for chronic use |

*6-MAM, the specific metabolite is detected only for 6 hours.

sensitivity and specificity. Lowering the cutoff increases sensitivity, although it also increases the potential for false-positive results by decreasing specificity.

#### 3.2.1.2 Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics

Understanding the basic principles of drug pharmacokinetics is crucial in evaluating patient adherence with opioids. Opioids administered by multiple routes, such as oral, transdermal, or intrathecal, showed variable pharmacokinetics. Absorption, distribution, metabolism, and excretion of drugs vary among patients and can vary day-to-day within a given patient – interindividual variability and intraindividual variability. Most of the pharmacokinetic variability is due to environmental and genetic factors, with drug formulation being a less likely source of variability (53). In contrast, pharmacodynamic response (effect of the drug on the body), variability in receptor configuration and sensitivity might affect response to opioids. While pharmacokinetics have been well studied, pharmacodynamic variability has not been studied well and is poorly understood.

#### 3.2.1.3 Absorption and Distribution

Absorption and distribution vary from patient to patient and thus similar doses do not result in similar systemic exposure (i.e., drug concentration at the site of effect), or similar pharmacologic effect. It has been shown that morphine shows approximately a 2.5-fold interindividual variability in oral (162), buccal (162,163), sublingual (162), and intramuscular absorption (164). In contrast, with limited first pass metabolism, oral oxycodone exhibits at least a 1.5-fold variability in absorption (165). Significant variability also has been described for hydromorphone and meperidine with first pass effect (metabolism of the drug in the gut or as it passes through the liver immediately after gut absorption), resulting in a widely variable amount of the drug reaching the systemic circulation (166). Further, for orally administered drugs, metabolism via glucuronidation, or phase II metabolism, might occur at the site of absorption (i.e., the intestine) and in the liver, resulting in reabsorption into the blood with enterohepatic recirculation (167) with excretion of glucuronides into the bowel and deconjugated. However, the first pass effect results in a significant reduction in the amount of the parent drug that reaches the systemic circulation, which is variable for multiple opioids. Consequently, without blood concentration data, the quantity of the excreted parent drug in urine will not provide unequivocal evidence of patient compliance with the recommended dosing.

Further, transporters can be involved in controlling the movement of medication across the intestinal lumen, hepatocyte membranes (influencing biliary excretion), and the blood brain barrier (53), thus influencing the rate of drug absorption, excretion, or arrival at the site of action (168). It has been suggested that transporter genetic polymorphism, along with potential environmental effects, can result in significant interindividual variability in drug absorption and distribution and thus efficacy of opioids (169).

#### 3.2.1.4 Metabolism, Transport, and Receptor Affinity

Multiple enzymes are considered to be involved in the phase I enzymes such as cytochrome P450 enzymes or CYPs and phase II enzymes such as UDP-glucuronosyltransferases (UGT), both of which exhibit genetic polymorphism, essentially categorizing the patients as poor metabolizers, intermediate metabolizers, extensive or "normal" state metabolizers, or ultra-rapid metabolizers with higher than normal metabolism (170). Phase I polymorphic enzymes such as CYP2D6, CYP2C9, and CYP2C19 impact drug effect by determining whether an inactive prodrug such as codeine can be converted to an active drug such as morphine. In addition, blood concentrations of the active drug are also influenced by genetic polymorphism by metabolism and clearance. Consequently, if a patient is classified as an ultrarapid metabolizer for CYP2D6, the enzyme that converts the prodrug codeine into the active drug morphine, it is expected that this person would require lower total daily doses of codeine to achieve the similar exposure of blood concentrations of morphine as that of an extensive metabolizer (171). The opposite applies for a poor metabolizer requiring higher doses of codeine to achieve similar exposure. Multiple CYPs are involved in metabolizing opioids, as illustrated in Table 2, which shows frequently used opioids in their metabolic routes (53,166,172-178). Individual genotype plays an important role in determining the rate of metabolism and the efficacy of a specific dose for particular opioids, resulting in findings that the dose of a drug might not correlate with the extent of pain relief or urine drug concentration, sometimes even within the same individual between testing periods (179). One of the drugs most commonly affected by CYPs is methadone. The R-enantiomer of methadone, thought to be primarily responsible for its

Table 2. *Frequently used opioids and their metabolic routes.*

| Drug | CYP1A2 | CYP2B6 | CYP2C19 | CYP2D6 | CYP3A | UGT | Demethylation | Glucuronidation | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Codeine | | | | ++++ | | + | | | (172,173) |
| Hydrocodone | | | | +++ | + | | +++ | | (173) |
| Hydromorphone | | | | | +++ | | | +++++ | (166) |
| Meperidine | | | | | | | + | | (179) |
| Methadone | | | | | | | +++++ | | (174) |
| R-methadone | | +++++ | + | + | + | | | | (175) |
| S-methadone | | +++++ | + | | + | | | | (176) |
| Oxycodone | | | | +++ | ++ | | +++++ | | (176) |
| Tramadol | | + | + | +++ | + | | ++ | | (177,178) |
| CYP indicates cytochrome P450; UGT, UDP-glucuronosyltransferases. | | | | | | | | | |

Adapted from: Nafziger AN, Bertino JS. Utility and application of urine drug testing in chronic pain management with opioids. *Clin J Pain* 2009; 25:73-79 (53).

analgesic effect, is metabolized by hepatic N-demethylation via CYP2B6; to a lesser extent, it is metabolized by intestinal CYP3A(174,180,181). Further, methadone exhibits a 30-fold variability in blood concentrations for a given dose (182,183) and methadone also has been shown to inhibit its own metabolism via the CYP enzymes (174,181).

CYP2D6 has been shown to metabolize codeine from prodrug to active drug morphine (184) and it also has been shown to have a minor role in metabolizing tramadol to the active O-desmethyl-tramadol.

Polymorphic enzymes such as CYP2D6 are reported to have 6-fold to 41-fold interindividual variability (184,185) and 17% to 122% intraindividual coefficient variability (186). Finally, patients with genetically determined increased drug metabolizing enzyme activity might be at greater risk for inhibitory drug interactions that can result in acute, excessive drug exposure (187).

The enzymes which do not show genetic polymorphism also can exhibit a wide range of individual variability in activity. CYP3A isozyme activity is associated with metabolism of alfentanil and fentanyl and might show significant variability in dose requirements and responses (188) due to a 2-fold to 10-fold interindividual variability (189,190).

In Phase II metabolism, UGT enzymes are involved, which affect metabolism of a number of opioids, including morphine and codeine.

In addition to drug metabolizing enzymes, transporters also play an important role in opioid response, with a 10-fold variability (191). There are also wide differences in the doses of opioids required for pain management, based on individual disease state, extent of the disease, and comorbid conditions. It also has been indicated that environmental factors including diet can affect the transporters, either by inhibition or induction of the transporters, thus providing fluctuations in drug concentrations (192).

Urine pH also has significant influence on drug concentrations excreted in the urine. A high protein diet results in acidic urine (193), whereas a vegetarian diet can result in alkaline urine (193,194). In addition, underlying disease states such as diabetes mellitus, respiratory or metabolic acidosis, or uremia can also cause an acidic urine pH of less than 6. Urinary tract infections with ammonia-forming bacteria cause an alkaline urine pH above 8.

The excretion of methadone is dependent upon urinary pH with higher concentrations of the parent compound methadone being excreted at lower urine pH, whereas urinary excretion of methadone metabolite EDDP (2-ethylidene 1,5-dimethyl 3,3 diphenylpyrrolidine) is not dependent upon urinary pH (180). It has been recommended that EDDP concentrations may be used to evaluate compliance with chronic, stabilized methadone therapy via UDT, instead of the parent compound methadone (180). However, the value or validity of this has not been established.

### 3.3 Laboratory Technology Used in Urine Drug Testing

Two types of urine drug tests are typically used: immunoassay and laboratory-based specific drug identification such as gas chromatography/mass spectrometry (GC/MS), liquid chromatography tandem mass

spectrometry (LC/MS/MS) or high performance liquid chromatography (HPLC). Enzyme-mediated immunoassay (EIA) is frequently used as the initial evaluation for UDT, which can test for numerous drugs or drug classes, and can determine if a class of substances is present or absent. In most cases, EIAs demonstrate adequate sensitivity but are not specific. They cannot equivocally identify a specific analyte and can result in false-negatives by missing compounds such as oxycodone, methadone, and fentanyl (195,196). Further, they also fail to distinguish between different drugs of the same class (e.g., opioids) and can produce false-positive results from cross-reactivity with other substances (e.g., quinolone antibiotics or any compound with similar structural and chemical properties to the original substance). Table 3 illustrates various drug cross-reactants. In addition, EIAs exhibit cross-reactivity with other commonly available medications such as over-the-counter diet agents and decongestants. Thus, confirmatory testing is required when an immunoassay is initially used and provides both high sensitivity and high specificity to reduce false-positives and false-negatives.

Multiple publications have shown not only high rates of inappropriate drug use in the chronic pain population, but also have identified multiple reasons for confirmatory testing along with differences in cutoff levels. Further, metabolic variations also have suggested for confirmatory testing (197). In a retrospective analysis of screening for non-compliance, in the data collected in almost a million patients, test samples showed that 75% of patients were unlikely to be taking their medications in a manner consistent with their prescribed pain regimen (158). This evaluation showed that 38% of patients were found to have no detectable level of their prescribed medication, 29% had a non-prescribed medication present, 27% had a drug level higher than expected, 15% had a drug level lower than expected, and 11% had illicit drugs detected in the urine (158). Further, it has been suggested that the lowering of the federally mandated cannabinoid immunoassay cutoff from 100 to 50 µg /L increased efficiencies and sensitivities for all immunoassays, with minor decreases in specificity (198). Consequently, the cutoff levels, which have been reduced to 20 and 15, further increases true-positive rates.

To identify individual drugs and metabolites, laboratory testing is recommended. Thus, a urine screen that is positive for hydromorphone in a patient receiving hydrocodone does not reflect drug abuse, but rather the appropriate metabolite of hydrocodone. Similarly, since codeine is metabolized to morphine, a screen that is positive for morphine in a patient taking codeine would be expected (199). Historically, there have been instances in which physicians who were not familiar with opioid metabolism have wrongly accused patients of drug abuse (197). Table 4 illustrates metabolites of opioids (199,200). In addition, prevalence of morphine metabolism to hydromorphone in chronic pain patients treated with morphine also has been established (197). It is also essential to note that

Table 3. *Drug cross-reactants*.

| **Drug Cross-Reactants** | |
|---|---|
| Drug | Cross-Reactant |
| Cannabinoids | NSAIDs, Marinol, Protonix |
| Opioids | Poppy seeds, chlorpromazine, rifampin, dextromethorphan quinine |
| Amphetamines | Ephedrine, methylphenidate, trazodone, bupropion, desipramine, amantadine, ranitidine, phenylpropanolamine, Vicks Vapor Spray |
| PCP | Chlorpromazine, thioridazine, meperidine, dextromethorphan, diphenhydramine, doxylamine |
| Benzodiazepine | Oxaprozin (Daypro), some herbal agents |
| ETOH | Asthma inhalers (sometimes) |
| Methadone | propoxyphene, Seroquel |

Gas chromatography should confirm all positives; screening detects a presence or absence, not the concentration. Drug tests are not quantitative.

Source: Manchikanti L, et al. Protocol for accuracy of point of care (POC) or in-office urine drug testing (Immunoassay) in chronic pain patients: A prospective analysis of immunoassay and liquid chromatography tandem mass spectometry (LC/MS/MS). *Pain Physician* 2010; 13:E1-E22 (49).

Table 4. *Metabolites of opioids*.

| OPIATE | METABOLITES | COMMENT |
|---|---|---|
| Hydrocodone | Hydromorphone<br>Dihydrocodeine<br>Normorphine<br>Norhydrocodone<br>Hydrocodol<br>Hydromorphol | If codeine to hydrocodone ratio < 10, codeine is not the sole source<br><br>Level generally lower than its hydrocodone source and below detection if only codeine was ingested |
| Oxycodone | Oxymorphone<br>Noroxycodone<br>Oxycodols and their respective oxide | |
| Morphine | Hydromorphone (minor)<br>Morphine-3-glucuronide<br>Morphine-6-glucuronide<br>Normorphine | If codeine to morphine ratio < 6, codeine is likely not the sole source<br><br>Level generally lower than its hydrocodone source and below detection if only codeine was ingested |
| Methadone | 2-Ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine<br>2-Ethyl-5-methyl-3, 3-diphenylpyrrolidine | |
| Hydromorphone | Dihydromorphine<br>Hydromorphone-3-glucuronide | Level generally lower than its hydrocodone source and below detection if only codeine was ingested |
| Oxymorphone | Oxymorphone-3-gluucornide<br>Oxymorphol | |
| Codeine | Hydrocodone (minor)<br>Norcodeine<br>Morphine | If codeine to hydrocodone ratio < 10, codeine is not the sole source<br><br>If codeine to morphine ratio < 6, codeine is likely not the sole source<br><br>Level generally lower than its hydrocodone source and below detection if only codeine was ingested |
| Propoxyphene | Norpropoxyphene | |
| Fentanyl | Norfentanyl | |
| Tramadol | O-desmethyl-tramadol<br>Nortramadol | |
| Butorphanol | Hydroxybutorphanol<br>Norbutorphanol | |
| Buprenorphine | Norbuprenorphine<br>Norbuprenorphine-3-glucuronide<br>Buprenorphine-3-glucuronide | |
| Heroin | Morphine<br>Codeine (contaminant)<br>6-Monoacetylmorphine | |

Source: Manchikanti L, et al. Protocol for accuracy of point of care (POC) or in-office urine drug testing (Immunoassay) in chronic pain patients: A prospective analysis of immunoassay and liquid chromatography tandem mass spectometry (LC/MS/MS). *Pain Physician* 2010; 13:E1-E22 (49).

metabolism of codeine, while it occurs in the majority of patients to morphine, a minority of patients are unable to make this metabolic conversion in the liver, due to a genetic deficiency of the cytochrome P-450 2D6 enzyme (201). In some cases this is because the patient is taking a medication with significant 2D6-inhibiting properties such as fluoxetine or paroxetine (202). Generally it has not been assumed that hydromorphone is a metabolite of morphine in humans (203), even though it has been found in several animal species given morphine (204). However, it has been demonstrated that hydromorphone might also be a minor metabolite of morphine in humans (205). In the past, it has been misconstrued that the presence of hydromorphone in patients taking morphine is an indication that the patient was either taking hydromorphone or hydrocodone (206). Further, one study (197) also demonstrated that hydromorphone was present in 21 of 32 cases (66%), and all patients were without a history of aberrant drug behavior. Positive cases occurred more frequently in women in those taking higher daily doses of morphine, and in those with higher urine morphine concentrations.

### 3.4 Diagnostic Accuracy

Diagnostic accuracy evaluations comparing immunoassay testing with chromatography have not been performed frequently in a prospective manner; however, there are multiple reports with retrospective evaluations. Manchikanti et al (207) prospectively studied the diagnostic accuracy of POC testing with immunoassay, comparing it with laboratory testing with chromatography in 1,000 patients. Compared with laboratory testing for opioids and illicit drugs, immunoassay in-office testing at high specificity and agreement, but variable sensitivity, demonstrates the value of immunoassay drug testing, but a cautious approach is advocated. Agreement for prescribed opioids was high with the index test (80.4%). The reference test of opioids improved the accuracy by 8.9% from 80.4% to 89.3%. Overall, results showed a necessity for 32.9% of the specimens to be sent for a reference test confirmation due to either abnormal opioid or illicit drug results. The abnormal specimens of patients receiving opioids improved the accuracy by 8.9% from 80.4% to 89.3%; for illicit drugs, the index test false-positive rate was 0% for cocaine, whereas it was 2% for marijuana, 0.9% for amphetamines, and 1.2% for methamphetamines. There was only a slight improvement in the accuracy data with laboratory intervention utilizing chromatography.

### 3.5 Identification of Adulteration or Subversion in Urine Drug Testing

Ensuring the validity of UDT is an important aspect of the evaluation of a chronic pain patient. Shortcomings of UDT include both false-positive and false-negative results. Federal programs have a number of safeguards in place in order to minimize laboratory errors. Consequently, for purposes of federally regulated drug testing, interpretation of a positive drug test requires a special expertise. Sadly, a number of modalities are available to defeat the purpose of UDT. The simple strategies to defeat UDT rely on dilution of the sample to lower the concentration of the drug in the urine specimen to a level below what it takes for a test to be reported as positive or stating that they have been passing too much urine. Facilities for detection of diuretics are not available in chronic pain management settings. Further, acute water intoxication has been reported as a complication of UDT in the workplace (208).

In chronic pain management settings, it is also possible for the urine specimen to be substituted. Multiple products are also available on the internet including freeze dried clean urine that can be reconstituted. Devices such as the "Urinator" allow these products to be quickly reconstituted and warmed to body temperature for delivery by a tube hidden in the clothing in both male and female donors. These can be hidden during casually observed collection. In extreme cases, it has been reported that people even use a prosthetic penis, catheterize themselves and instill someone else's urine, and adulterate urine by "Urine Luck" (209). Some in vitro adulterants act by interfering with the immunoassay detection, whereas others convert the target drug to compounds that do not bind to the antibodies used in the immunoassays or that produce negative results in subsequent confirmation testing (210). Commercial products are available to assist an individual in "passing a drug test." "Urinaid" was one of the earliest products, with an active ingredient of glutaraldehyde, which interfered with screening immunoassays by producing final absorbance rate readings that were lower than those true-negative urine samples (211).

Use of niacin also has been described to use to defeat UDT (212). No scientific evidence indicates that taking niacin can alter a urine drug test result. However, readily accessible information on the internet lists ingestion of niacin as a way to prevent detection of THC, the main psychoactive ingredient of marijuana.

## 4.0 Practical Aspects

In clinical settings, UDT is utilized for compliance, as well as forensic testing to monitor therapeutic activity, misuse, and illegal drug use (76,103-108,110,111,213,214). Consequently, the initial and confirmatory testing levels, as well as the number of drugs tested, can be customized and are usually different from those evaluated under federal testing programs.

Drug screening can be an important tool to ensure patient compliance with prescription regimens. Drug screening or testing can be effectively performed in the physician's office using point of care (POC) urine (dipstick immunoassay) testing. However, practitioners using POC testing need to be aware of whether the system used is compliant with methods and assurances established by the Clinical Laboratory Improvement Advisory Committee (CLIAC). A Clinical Laboratory Improvement Amendments (CLIA) waiver is required to perform certain tests including urine immunoassay. Only immunoassay tests for certain drugs are CLIA waived, and these may be performed in the office only if and when a certificate of waiver is first obtained by the physician or facility. Generally these tests do not require extensive training for office personnel.

UDT has become the standard of care for patients on controlled substances; however, the relative value of in-office screening and laboratory confirmation of those tests is sometimes unclear or controversial for physicians. The POC manufacturers recommend that their test needs to be confirmed; however, advantages and cost benefits have not been evaluated and confirmed independently.

Of particular concern to clinicians in this context of UDT is that the cost of UDT in the office, followed by a confirmatory test, can be expensive, with costs ranging from $250 to $1,400 (49,51,68,69,110,111, 215). The Centers for Medicare and Medicaid Services (CMS) have recently changed codes for UDT from the old code (80101) used by pain physicians to a new code (G0431) effective January 10, 2010 (215). This action has been taken by CMS due to excessive use of UDT and abuse (49,51,68,69,110,111). While the earlier code included chromatographic methods and its descriptions, the new G-code descriptor states, "drug screen, qualitative; single drug class method (e.g., immunoassay, enzyme assay), each drug class" and excluded chromatography (216). This has caused significant discussion, debate, and problems for many of the physicians who depend on the extra income and also the manufacturers of POC sets and laboratories.

At present, there are no validated studies to evaluate the diagnostic accuracy, value, and validity of UDT in POC settings compared to laboratory settings.

## 5.0 An Algorithmic Approach for Urine Drug Testing

An algorithmic approach is developed based on evidence; however, for UDT including accuracy, validity, and cost effectiveness, there continues to be a paucity of evidence (1,207,213-223). Even so, UDT is one of the simplest and least invasive approaches to biological sample screening in analyzing for drugs and their metabolic products, when cost effective appropriate principles are utilized.

A step-wise process for UDT may be performed as a baseline measure of risk, as well as monitoring for compliance. UDT must be performed utilizing appropriate principles and the results must be interpreted based on available scientific evidence.

### 5.1 Baseline Urine Drug Testing

UDT is helpful in establishing the reliability of patients' reported substance use. It is becoming more and more frequent that many physicians, specifically in pain management settings, believe that UDT should be used routinely to establish baseline information regardless of how much information is available from physicians, prescription monitoring programs, and other sources. The advantage of a universal approach is that all patients are treated in a similar fashion, thus making it a routine part of the evaluation, the same as measuring blood pressure or other vital signs, and destigmatizes the drug testing itself. Because of the cost, some believe that it must be selective, whereas others believe that it should be universal and that not only POC testing should be done, but lab testing must also be included. The majority of patients might have predicted results while some will have unexpected results. A discussion may be carried out with the patient and a repeat test may be planned with immunoassay in an office setting with the next visit. The only indication for laboratory testing is a patient's denial and insistence on proof. It is important in modern settings to perform baseline drug testing since a large proportion of patients (> 90%) have been exposed to opioids and other controlled substances prior to arriving at interventional pain management or pain medicine settings.

## 5.2 Monitoring for Compliance

In the therapeutic phase of chronic pain management, either during the initiation, titration, or maintenance of opioid treatment, UDT can be useful in detecting non-compliance, unauthorized drug use, doctor shopping, and diversion. Multiple investigators have studied the importance of UDT and adherence monitoring. They found positive evidence for reducing prescription drug abuse, as well as illicit drug use (16).

There is no evidence to guide physicians on identifying chronic pain patients who should have UDT and how often. Multiple descriptions have been provided. Some recommendations include patients' risks for opioid misuse and addiction and aberrant drug-related behaviors.

A practical approach would include baseline drug testing, if appropriate; initiation of opioid therapy and compliance monitoring within one to 3 months after baseline monitoring; and routine, random monitoring approximately every 6-12 months or so, with provision for monitoring for unexpected results, complaints, or behavior patterns.

Thus, the majority of patients will receive a baseline test, initiation of the compliance test, and one year monitoring within the first 15 months or so. After that, if the patient is continuing with a pain management program, testing will only be required once a year. However, patients with abnormal results will require more frequent testing based on the results and the philosophy of the prescribing physician.

## 5.3 Interpretation of the Results

Appropriate interpretation of the results is crucial. UDT can only assist clinic decision-making; it should not be considered as definitive. There are new multiple limitations and restrictions on interpreting UDT. Thus, a thorough knowledge and full patient history are essential, including an appropriately collected sample and prevention of tampering. Other limitations include the gaming of the system, where patients know when the evaluation will be performed, thus they alter their drug utilization. However, abnormal or unexpected results should be interpreted with caution. In general, 5 scenarios can be faced when interpreting UDT results:

1) UDT positive for prescribed drugs and negative for any other drugs –illicit or licit;
2) UDT negative for prescribed opioid;
3) UDT positive for non-prescribed opioid or benzodiazepines;
4) UDT positive for illicit drugs;
5) UDT specimen tampered with low urine creatinine or cold urine sample.

### *5.3.1 Normal Urine Drug Testing Result*

This result illustrates appropriate intake of the provided medication and lack of intake of any other drugs. In these situations, a patient may be tested with the usual testing of initiation of compliance monitoring and once a year with 3 tests performed during the first 15 months and once each year later on.

### *5.3.2 Urine Drug Testing Negative for Prescribed Opioid*

Potential explanations for such a result include non-compliance with irregular intake of opioids, diversion, or false/negative results.

Appropriate action would be repeating the test using laboratory testing for specific drugs of interest, along with a history regarding non-compliance and diversion, more stringent compliance monitoring including frequent pill counts, fewer pills prescribed with each prescription, and discussion of possible termination of opioid therapy with future repeated negative UDT.

### *5.3.3 Urine Drug Testing Positive for Non-Prescribed Opioid or Benzodiazepines*

The explanation would be either the results are false-positive or the patient acquired opioids from other sources or doctor shopping.

In such cases, UDT may be repeated with immunoassay and confirmed with the laboratory. Prescription drug monitoring program record can be obtained or pharmacies and physicians may be contacted to verify if the patient has actually received other opioids from different providers. If so, patient education and reiteration of opioid agreement with the patient are appropriate. Another possibility would be that the patient might have received certain benzodiazepines as preoperative sedative measures, which could be confirmed from taking a thorough history.

### *5.3.4 Urine Drug Testing Positive for Illicit Drugs*

Illicit drugs are used by approximately 10% of patients in chronic pain management settings. The possibilities of such a result include that the patient might have occasionally used or is a frequent user, or is addicted to the illicit drug. It is well accepted that patients who use illicit drugs are at increased risk for opioid misuse, abuse and diversion. Therefore, such patients should be informed and advised that continued illicit

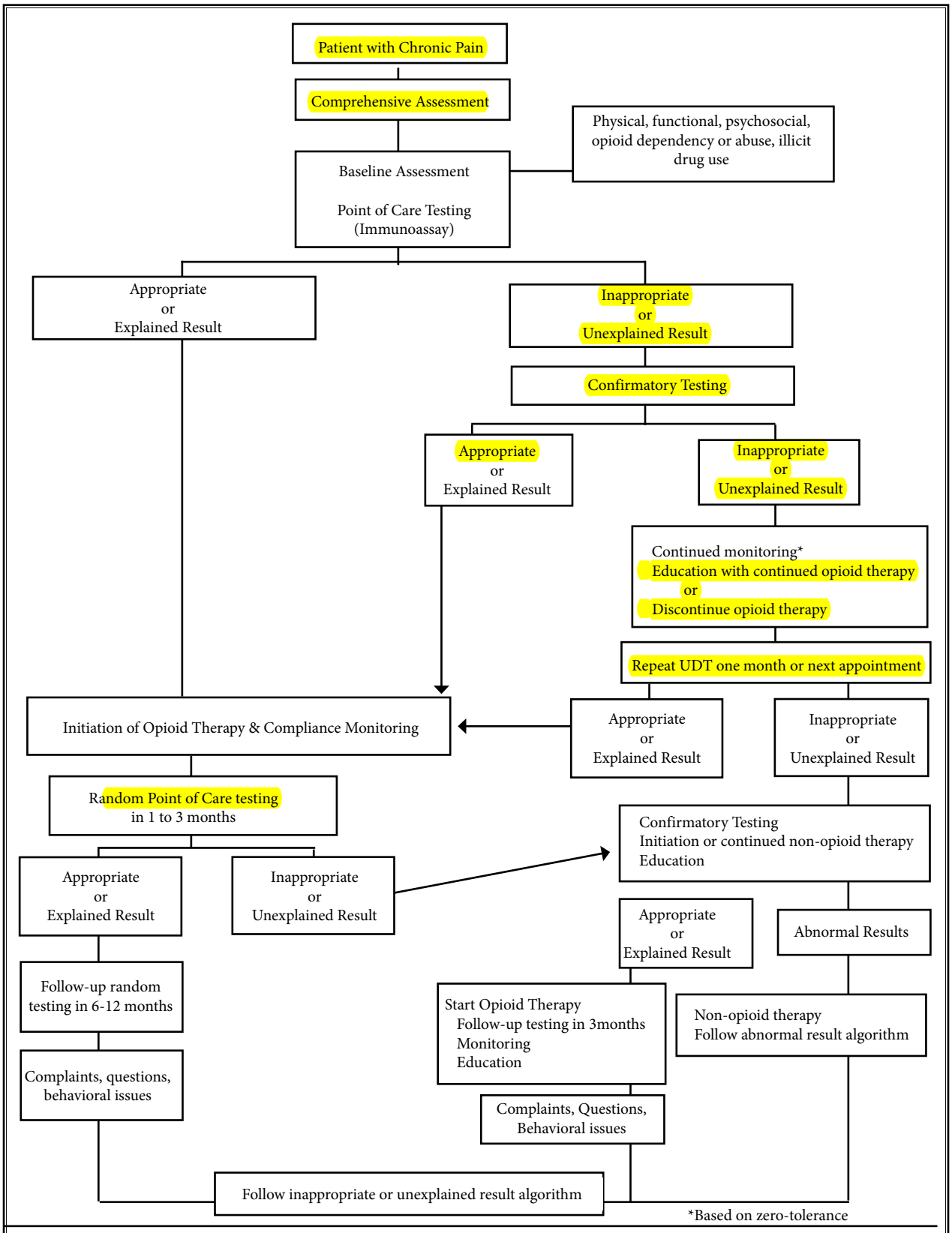


Fig. 1. *Algorithmic steps in urine drug testing in chronic pain.*

drug usage is incompatible with opioid therapy.

The appropriate action would be to reiterate opioid agreement with the patient, to inform the patient that continued illicit drug use prohibits opioid therapy, to repeat UDT with confirmation test on a regular basis, and failure to comply with this would result in termination of opioid therapy.

However, there is a difference of thresholds held by different practices, which results in different practice philosophies that dictate the level of tolerance when faced with such actions, i.e., "one chance" or "zero tolerance."

#### *5.3.5 Sample Tampering*

Initially, all explanations should be ruled out. Almost all explanations are incriminating – either the patient added water to the sample, or there was a delay in handling the sample, which is unusual.

Appropriate actions include repeat UDT with a supervised collection. Appropriate steps also include appropriate history and education.

At all steps, other tools of adherence monitoring must be utilized, including inquiries with doctors, pharmacies, and drug monitoring programs. Meanwhile, a physician should also pay attention to the information provided by insurers with duplicate prescriptions and insurer's issues related to excessive use or inappropriate use of drugs.

Figure 1 illustrates the algorithmic steps in UDT.

### 5.4 Managing Patients with Abnormal Urine Drug Testing

When a physician is presented with abnormal results in a patient, appropriate action must be taken. The action does not mean zero tolerance and discharging each and every patient, however, the physician has to look into various other issues related to perceived or actual abuse based on undertreatment of pain, opioid hyperalgesia, worsening disease process, and onset of new problems. A patient may still be continued and managed with interventional techniques without controlled substances if it becomes essential to do so. Interventional techniques have been shown to be effective in chronic pain, and also might reduce the dosage, multiple side effects, etc. (75,112-128,132,133,224-226).

## 6.0 Conclusion

In general, a diagnosis of drug abuse should never be made based on the results of urine toxicology alone. It should be considered within the context of aberrant medication use, drug-seeking behaviors, and unimproved or declining function (49,69). Despite their limitations, UDTs provide additional information beyond behavioral monitoring

UDT represents a useful adjunctive testing mechanism that should be strongly considered in tandem with other forms of patient monitoring, such as regular follow-up visits, behavioral observation, risk assessment, and reviewing prior history of addiction or substance abuse. While its role should not be overstated, physicians should avoid making judgments about patient compliance based solely on the results of a urine test. Urine testing is currently underutilized in the clinical setting and should be considered part of an integrated drug compliance regimen (51).

Based on the recent results of the diagnostic accuracy of urine drug testing, in a worst case scenario, it appears that one would have to send 32.9% of patients specimens to the lab because of abnormal results; however, utilizing a common sense approach, this can be reduced substantially to 20% or lower, which will save substantial amounts of health care expenses. Each time a physician orders a drug test from the lab, he or she should realize that the cost of this is going to be higher than the cost of most of the interventional techniques we will be performing on these patients.

The future of UDT compliance and adherence monitoring of opioids depends on appropriate use based on evidence-based medicine principles. It is essential to evaluate the appropriate literature based on principles of evidence-based medicine and comparative effectiveness research, first and foremost showing the effectiveness of opioids, followed by studies illustrating the accuracy and value of any compliance monitoring, including UDT (217-221).

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