

# The Debate on Urine Drug Testing in Pain and Addiction Management: Coverage or Non-Coverage?

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Chronic pain is pervasive and costly. Based on a recent report published by the Institute of Medicine (IOM), it is estimated that chronic pain affects 100 million American adults, which is more than the total affected by heart disease, cancer, and diabetes combined. Pain costs the nation up to \$635 billion each year in medical treatment and lost productivity [1,2].

Opioids/Opiates have been used for centuries and remain the most potent and reliable analgesic agents [3]. Their usage has recently increased, in part because providing adequate pain relief is now considered an important standard of care and is required by law in some states. While there is no debate over the short term use of opioids, their use for chronic non-malignant pain is controversial and there is growing reluctance among some physicians to prescribe them [4]. The problem is the most powerful opioid analgesics are the most liable to cause misuse, abuse, addiction, and diversion.

Should opioids be used in patients with non-malignant chronic pain? Or, will patients with non-malignant chronic pain be harmed if opioid analgesics are withheld for concerns of misuse, abuse, addiction, or diversion?

Despite the lack of convincing data for long term efficacy and the growing problem of prescription abuse, many physicians prescribe opioid analgesics for patients with chronic non-malignant pain. The reasons are complex, but many believe that it is unconscionable to withhold adequate treatment from any patient complaining of severe pain, whatever the cause, especially when alternative treatment has failed.

In 2009, the American Pain Society and the American Academy of Pain Medicine issued joint guidelines recommending the judicious use of opioid analgesics when chronic non-cancer pain is moderate or severe, when it has an adverse effect on function or quality of life, and when a careful risk-benefit assessment indicates a likely net benefit [5].

Also in 2009, the American Geriatric Society issued guidelines on persistent pain in the elderly, which placed opioids as a second-line choice for pain management after paracetamol, and stated that "all patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy" [6].

More recently, in the March 2013 issue of The American Journal of Medicine, de Leon-Casasola opined that "For older adult patients at higher risk for NSAID-related adverse effects, such as those who have gastrointestinal or cardiovascular disease, diabetes mellitus, or who are taking low-dose aspirin, opioids are recommended instead. Opioids may also be an appropriate option for patients with neuropathic pain who have not achieved adequate analgesia from maximum doses of first- and second-line anti-neuropathic agents." [7].

Indeed, in the context of expanded pain care, opioid consumption levels have tripled globally since 1990 [8]. In the USA, the total amount of opioids prescribed, measured in morphine-equivalent doses (MEDs), increased more than 600% between 1997 and 2007. More than 200 million opioid prescriptions are now written every year [9]. Undeniably, the United States is facing an epidemic of prescription drug misuse and diversion, resulting in increased rates of addiction, health care

utilization, and overdose deaths. Prescribed opioids constitute the main supply of these drugs for 70% of opioid abusers [10]. Accidental overdose deaths underscore the seriousness of this problem. Nationally, the rate of unintentional deaths due to prescription drug overdoses has nearly tripled over the past 10 years. In 2010 approximately 16,000 overdose deaths were attributed to prescription opioids [11]. The relatively recent dramatic rise in the misuse and diversion of prescription medications, as well as in rates of addiction and overdose deaths, prompted increases in drug testing, which are now spreading into other areas of medicine outside addiction treatment and pain management.

Urine drug testing plays a vital role in the detection of opioid misuse and the evaluation of patients with opioid intoxication. Urine drug testing uses both immunoassay (IA) and chromatographic methods (e.g., liquid chromatography with mass spectrometry (LS/MS)), often in combination, to yield high detection sensitivity and drug specificity. Testing methods for opioids originated in the workplace-testing arena and focused on detection of illicit heroin use. Analysis for a wide range of opioids is now required in the context of the prescription opioid epidemic [12].

In workplace opioid testing, detection of illicit drug use is sought in a population with a generally low prevalence of opioid use. In the clinical setting, the prevalence of drug exposure is much higher due to the preselection of patients for screening based upon clinical suspicion of drug exposure or prescription of the opioid drug. The purpose of testing may also be different in the clinical setting, where the goal is often to detect nonuse of a prescribed opioid drug that may indicate drug diversion, which is an important contributor to the ongoing prescription opioid drug epidemic. These differences in prevalence and testing goals/ have an important impact on the utility of testing [12,13].

The IA and GC/MS paradigm of workplace drug testing worked reasonably well in medical settings in the 1990s, when nearly all patients with substance use disorders used a fairly limited menu of drugs. As a growing array of prescription drugs and designer drugs became available, the drug testing challenge was no longer to identify a handful of drugs, but rather to identify the scores of continually evolving compounds taken by drug users [14].

IA, performed either in the laboratory or at the POC, relies on competitive binding of an antibody to detect the presence of a particular drug or metabolite in the urine. Opiate.

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IA typically use morphine as a single calibrator drug to set the threshold for distinguishing a “positive” or “negative” test result. IA is considered a “qualitative testing”. Due to the limited cross-reactivity of antibodies with the diversity of opioid drugs, urine specimens containing many drugs may escape detection by opiate immunoassays. IA techniques are convenient because they provide rapid results (less than 5 minutes). A major limitation of IA testing is that it fails to distinguish drugs of the same class. Therefore, aberrant drug-taking behavior within the same drug class would not be detected. In addition, IA cross-reactivity across a drug class is limited, especially in the case of opiates, benzodiazepines, and barbiturates. For example, opiate immunoassay screens are typically targeted to codeine and morphine, while semisynthetic opiates such as hydrocodone and oxycodone may react only at high concentrations or not at all [15]. Morphine-specific opiate assays are insensitive to the synthetic opioids (e.g., methadone, buprenorphine, and fentanyl). Detection of these opioids requires assays that specifically target these drugs; commercial immunoassays are available for oxycodone, buprenorphine, fentanyl, and methadone and its metabolites [16].

In pain/addiction practice, it may be important to identify a specific opioid and not just the class. The gold standard in the UDT is the use of either gas chromatography/mass spectroscopy (GC/MS or GC/MS-MS) or LC/MS-MS to confirm test results. MS-MS refers to tandem mass spectroscopy, which provides greater sensitivity and specificity than single-stage MS [15]. GC/MS and LC/MS are considered “quantitative testing”.

Definitive testing following positive immunoassay (IA) results is needed in pain practice when it is important to identify the specific drug, not just the class of the drug. Definitive testing following negative immunoassay results is often needed, when the unexpected absence of a prescribed drug on an IA test is at odds with the patient’s account of medication use. Also, in a patient with a history of misuse or substance use disorder, periodic definitive testing of negative IA test results of specific drugs or metabolites is warranted [14].

One examination of LC-MS/MS results following an immunoassay point of collection (POC) testing in addiction treatment settings found high rates of clinically false negatives, that is, samples tested by POC were reported negative but LC-MS/MS results were positive. Twenty-nine percent of opioids other than methadone identified by LC-MS/MS were missed by POC tests; 28% methadone, 43% amphetamines, 35% benzodiazepines, 40% cocaine and 20% marijuana. Additionally, investigators found rates of office-based false positive results including 22% of opioids other than methadone identified as positive on POC but negative on LC-MS/MS, 46% methadone, 21% amphetamines, 61% benzodiazepines, 12% cocaine and 21% marijuana [17].

Testing in a population of drug users in whom determination of adherence with treatment is a significant concern sometimes requires more frequent testing, more extensive test panels, and more sensitive and specific testing techniques, although in many settings relatively inexpensive tests are useful. Testing in other specialized settings, such as pain management, addiction treatment programs, and professional health monitoring programs also may necessitate the use of larger and more extensive drug testing panels that require more advanced and expensive testing technologies.

Frequency of testing should be matched to patient risk. Every patient poses some, however small, risk for drug misuse, addiction, or diversion. Therefore all patients receiving chronic opioid therapy should be monitored with UDT. Risk should be assessed for every patient prior to and throughout opioid therapy. Patients with added risk factors for

opioid misuse – personal or family history of substance use disorders, psychiatric co-morbidities, and younger age (particularly males) – may warrant more frequent testing. Likewise, those patients who display problematic behaviors should be tested for-cause. It is reasonable for stable, low-risk patients to be tested infrequently but randomly [14].

Some existing guidelines recommend that high-risk patients be screened at least 4 times per year, up to every month, office visit, or drug refill, and that low-risk patients be randomly screened once or twice a year; moderate-risk patients should be screened on a schedule somewhere between these extremes. High-risk patients with aberrant behaviors require the most intense monitoring [18]. Patients considered at low to moderate risk who subsequently have aberrant UDT results or display aberrant behaviors should be moved into the high-risk category. The Official Disability Guidelines and The Utah Clinical Guidelines suggest more stringent monitoring [15,18].

It is the policy of the American Society of Addiction Medicine (ASAM) that the elements of drug testing be determined by the ordering physician based on patient-specific medical necessity. Arbitrary limits on reimbursement and restrictions on drug testing can interfere with a physician’s judgment and instill discriminatory limits on addiction care. The consequence and costs of not doing drug testing, or doing inadequate testing, may be substantial as physicians will forfeit potentially important information about their patients’ health status [14].

Further, we have to recognize that some people may suffer from iatrogenic opioid use disorders, and many of them who would not have met risk criteria when opioid therapy was initiated subsequently developed opioid use disorders [19,20]. Also, we must care for patients directly or indirectly harmed by opioid use, misuse, and diversion, as we know from opioid maintenance treatment, even dose reductions motivated by practice or policy changes may be hazardous, possibly increasing mortality even among patients who do not seek illicit opioids [19].

Urine drug testing, including IA and GC or LC/MS, should be considered as a primary preventative, diagnostic, and monitoring tool to identify the presence or absence of drug of abuse or therapeutic agents related to addiction management in multiple settings. Increasing the use of drug testing in both medical and nonmedical settings has the potential to improve public health by discouraging unhealthy or illicit drug use and by promoting early identification of substance use disorder. Drug testing provides opportunities for appropriate therapeutic interventions [14].

As stated previously, “qualitative” IA at POC are known to be flawed with “false positive” and “false negative” results [17]. Without the definitive result from a “quantitative test” such as LC/MS or GC/MS, it will be impossible for the prescribing physician to make appropriate clinical decision as “Positive IA” could be “false positive”, and “Negative IA” could be “false negative”. When a definite clinical decision is made based on the test result that lacks definite evidence, because of the “Non-Coverage Policy of the “quantitative test”, not only may the patient be wrongly accused “drug abuse/misuse/diversion”, resulting in patient’s discharge from the clinic, the physician may also subject himself or herself to lawsuits or complaint to the medical board, simply due to lack of valid, definitive evidence.

The critical difference between the two methods is that the “qualitative” method is easily tampered with especially by diverters but also by sophisticated addicts. A simple “yes” or “no” shows the presence

or the absence of the drug of interest. One popular method for diverters and sophisticated addicts is to either have "clean" or "washed" urine and then to "shave" the pill or medication they are supposed to be on into the urine. By doing this and using "qualitative" only, everything looks just fine. *Even if the patient or diverter is called in randomly to submit the test.* In addition to this it is impossible to tell if metabolites (by-products) are present in "qualitative" only which is a second way of knowing if a pill has been "shaved".

In summary, chronic pain is pervasive and costly. There is still widespread under-treatment of chronic pain despite the USA is facing a crisis of opioid endemic. Opioid analgesics should judiciously be utilized in treating moderate to severe chronic pain when other agents have failed. Because opioids are also liable for abuse, misuse, and addiction, stringent monitoring prior to and during the chronic opioid therapy is essential. Urine drug testing, including IA and GC/LS or LC/MS, are valuable tools for health care professionals to use, as part of a comprehensive evaluation of patients, in order to reach the correct diagnosis and to develop appropriate treatment, and monitoring plans. They are tools that can improve diagnosis and treatment, just as lab testing is a central component of most areas of health care to improve clinical accuracy and outcomes.

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