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Analysis and interpretation of drug testing results from patients on chronic pain therapy: a clinical laboratory perspective

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Abstract

Background: Recent guidelines recommend monitoring for opioid and drug use in patients with chronic pain to detect use of undisclosed or illicit substances, and to determine compliance with prescribed medications. We examined the technical and clinical impact of drug testing for patients on chronic pain therapy in our clinical laboratory.
Methods: Testing volumes were obtained for 4 years. Volumes from three recent months were also examined in detail to determine average turnaround time, assay performance (i.e., number of positive screening and confirmatory tests and testing discrepancies) and consistency of patient results with medication history.
Results: Our testing volume continues to grow significantly, especially in the primary care setting, with an average yearly increase of 34%. Approximately 70% of patients confirmed positive for an opioid. Other drugs were positive in $<30\%$ of patients. Twenty-nine percent of patients tested positive for a medication without a prescription. Overall, the compliance rate was 85% indicating that 15% of patients had negative test results despite being prescribed a chronic pain medication.
Conclusions: Clinical laboratories should consider the impact of these guidelines and examine options to optimize testing such as limiting or modifying the test panel.
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Keywords: chronic pain; clinical laboratory; opioids; pain clinic; urine drug testing.

Introduction

Current published guidelines recommend periodic monitoring for opioid and drug use in patients with chronic non-cancer pain (1, 2). According to these guidelines, drug testing should be performed to identify use of undisclosed substances, uncover diversion of prescribed substances, and determine compliance with prescribed substances. A specific testing panel is not recommended by these guidelines, and the time interval between testing depends on the specific circumstances of a given patient. Initial testing to detect illicit drug use may be performed using class-specific immunoassay panels that do not identify individual drugs within each class. However, the guidelines state that initial testing should be followed with a specific confirmatory technique such as gas chromatography/mass spectrometry or liquid chromatography/tandem mass spectrometry to identify, or confirm, the presence or absence of a specific drug and/or its metabolite(s).

Several articles have summarized drug testing results in chronic pain patients. These publications stress the need for stringent screening programs as recommended by recent guidelines (2–9). Michna and colleagues found that 45% of patients had urine results that were not consistent with their prescribed medications and 20% had illicit substances in their urine (8). The 2007 annual report from the American Association of Poison Control Centers confirms the high rate of abuse of analgesics and other substances in the population in general (10).

Clinical laboratories will be affected by these recommendations to varying degrees, depending upon their patient population and their clinical interpretation of the guidelines. Testing volumes, breadth of test menu, specimen processing requirements, turnaround time, result interpretation, and cost need to be considered. For example, many hospital laboratories have the capability to perform in-house urine drug screening for their emergency department, however, the components and cut-offs of screening panels may be different for patients on chronic pain therapy compared with emergency department patients. Also, it may not be feasible to perform the additional screening tests in-house (11, 12). Most laboratories do not have the resources to perform confirmatory testing and outsource this testing to a reference laboratory. Testing performed by reference laboratories is costly, especially when large numbers of confirmations are necessary. In addition, the demand for specialized testing increases to accommodate the prescribed medications.

In recent years, the clinical laboratory at Brigham and Women's Hospital, which services a large aca-

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demic medical center, has seen a marked increase in the number of requests for urine drug testing in patients on chronic pain therapy along with an expansion of the testing requested beyond that currently offered and performed in the laboratory. We reviewed the clinical and technical impact of drug testing on our clinical laboratory.

Materials and methods

The clinical laboratory at Brigham and Women's Hospital currently sends specimens from patients on chronic pain therapy to a reference laboratory for both initial and confirmatory testing. The pain clinic at Brigham and Women's Hospital manages the majority of patients on therapy for chronic pain, and in conjunction with the laboratory, has constructed an appropriate panel consistent with their interpretation of the recent guidelines (Table 1). Drugs such as benzodiazepines, fentanyl, methadone, opioids and tramadol are prescribed for chronic pain and are typically monitored to assess compliance or uncover potential diversion. We perform testing for all substances listed in Table 1 in order to discover the use of illicit or undisclosed substances. These substances may be obtained illegally by patients or may have been prescribed by a clinician other than the one ordering the testing.

The initial screening panel is performed by our primary reference laboratory using an enzyme multiplied immunoassay technique (EMIT) II plus (Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA) on an Olympus AU400e analyzer (Olympus America Inc, Center Valley, PA, USA). Qualitative screening results are reported for amphetamine, barbiturates, benzodiazepines, cocaine metabolite, ethanol, methylenedioxymethamphetamine (MDMA), methadone, opioids, phencyclidine (PCP), propoxyphene and tetrahydrocannabinol (THC). Corresponding screening cut-offs are listed in Table 1. In general, confirmations are performed by gas chromatography/mass spectrometry or liquid chromatography/tandem mass spectrometry only when screening results are positive. However, due to the low cross-reactivity of the opioid assay for oxycodone and oxymorphone, confirmations for opioids are performed on all patient specimens regardless of the screen results. In addition, a screening assay for 6-monoacetylmorphine (6-MAM) is performed only in patients with positive morphine results in order to evaluate recent heroin use.

We retrospectively examined the pattern of urine drug testing for patients on chronic pain therapy in our laboratory. Test volumes were gathered from January 2005 to December 2008. We included the percentage of tests ordered from our pain clinic vs. other areas, such as primary care. Three months (March, April and May 2008) were examined in more detail to determine average turnaround time, number of positive confirmatory tests, the number of false positive and false negative screening results and any testing discrepancies.

Correlations with patient medication and clinical history were performed using our electronic medical record to determine if results were consistent with prescribed medications. Considering drug metabolism pathways and differential specificity of the opioid screen assay, oxycodone and oxymorphone, morphine and codeine, and hydrocodone and hydromorphone were grouped together in the data analysis (Figure 1).

We took into account the technical performance of the assays when determining whether or not the clinical medication history was consistent with the test results. For example, when using the EMIT assay, patients taking their prescribed dose of clonazepam or lorazepam may have had a negative benzodiazepine screen result due to the low cross-reactivity of the assay for these medications. If a negative screening result in a patient prescribed a medication could be explained by the technical performance of the assay, the results were considered consistent. In addition, both negative and positive results in patients taking medications on an ''as needed'' basis were considered consistent. We could not take into account an inherent limitation of urine drug testing. Negative results even with highly sensitive, quantitative assays cannot confirm that a patient is not taking their prescribed medication. For example, patients with unusual drug metabolism such as that seen with genetic variations in drug metabolizing enzymes, can show

Table 1 Current test panel for patients on chronic pain therapy[a].

Test	Cut-off for screening test	Cut-off for confirmation test
6-MAM[b]	Not performed[c]	10 ng/mL
Amphetamine	**1000 ng/mL**	50 ng/mL
Barbiturates	**200 ng/mL**	100 ng/mL
Benzodiazepines	**200 ng/mL**	100 ng/mL
Buprenorphine	Not performed[c]	**5 ng/mL**
Cocaine metabolite	**300 ng/mL**	50 ng/mL
Ethanol	**10 mg/dL**	Not performed
Fentanyl	Not performed	**1 ng/mL**
MDMA	**500 ng/mL**	50 ng/mL
Methadone	**300 ng/mL**	100 ng/mL
Opioids	**300 ng/mL**	**100 ng/mL**
PCP	**25 ng/mL**	25 ng/mL
Propoxyphene	**300 ng/mL**	300 ng/mL
THC	**50 ng/mL**	3 ng/mL
Tramadol	Not performed[c]	**100 ng/mL**

[a]Screens and/or confirmations in bold-faced are performed on every specimen. Screens and/or confirmations not in bold-faced are performed under special conditions or when the screen is positive. [b]6-MAM is performed only in specimens, which are positive for morphine. [c]Screening assays are available, but were not performed. 6-MAM, 6-monoacetylmorphine; MDMA, methylenedioxymethamphetamine; PCP, phencyclidine; THC, tetrahydrocannabinol.

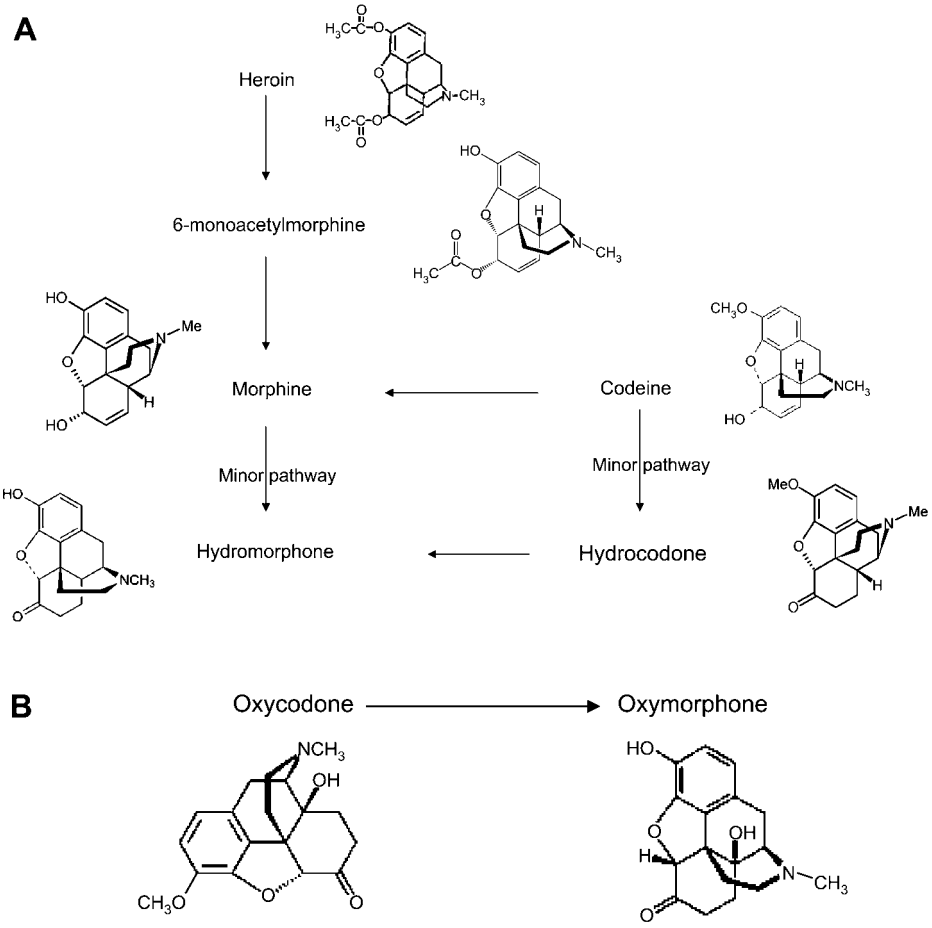

Figure 1 Opioid metabolism.
(A) Metabolic pathways of morphine and its derivatives. (B) Metabolic pathway of oxycodone and its primary metabolite.

negative screening results, despite compliance with medication use (13).

Results

The average turnaround time for all final results was 9.9, 11.1 and 9.6 days for March, April and May 2008, respectively. The test panel is extensive and includes assays such as buprenorphine, fentanyl and tramadol (Table 1) that are specific for monitoring pain management patients. Due to an increasing test volume, the number of specialized tests requested, and the fact that we do not perform testing in-house, the cost to our laboratory is high.

The test volumes have increased yearly from the pain clinic as well as from other areas of the hospital such as primary care (Figure 2). The number of specimens with orders for the chronic pain panel increased by an average of 34% per year from 2005 through 2008. The percentage of panels ordered by services other than the pain clinic increased significantly from an average of 3% in 2005, 2006 and 2007 to 10% in 2008.

The percentage of patients with both screen and confirmed positive test results for each drug or class of drugs was determined using 3 months of recent data (Table 2). Approximately 70% of patients confirmed positive for an opioid. Of these patients, 46% tested positive for oxycodone and/or oxymorphone, 24% tested positive for morphine and/or codeine and 17% tested positive for hydrocodone and/or hydromorphone. These results indicate that patients were taking multiple opioids simultaneously. Approximately 20% of patients were positive for methadone

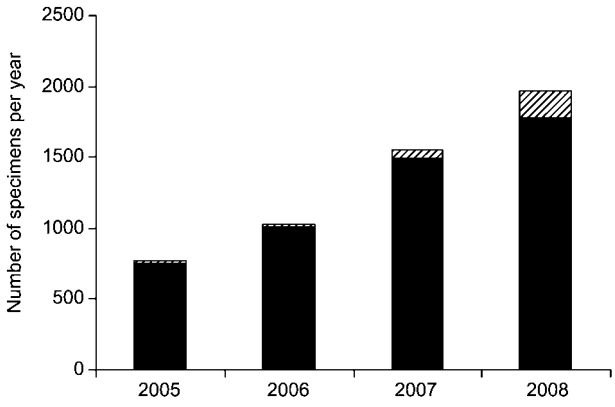

Figure 2 Yearly test volumes.
The yearly test volumes from our pain clinic (solid bars) and other hospital areas (diagonally striped bars) are plotted from 2005 to 2008.

Table 2 Patients testing positive by drug screening and/or confirmatory testing.

Drug	% of patients with a positive screening result (total number)[a]	% of patients with a positive confirmatory result (total number)[a]
Opioid	53.6 (218)	69.5 (283)[b]
Oxycodone, oxymorphone	31.0 (126)	46.2 (188)[b]
Morphine, codeine	23.6 (96)	23.8 (97)[b]
Hydromorphone, hydrocodone	17.2 (70)	17.2 (70)[b]
Methadone	22.1 (90)	21.9 (89)
Benzodiazepines	16.7 (68)	14.5 (59)
Fentanyl	Not performed	12.5 (51)
THC	6.1 (25)	6.1 (25)
Tramadol	4.9 (20)	Not performed
MDMA	4.7 (19)	0.0 (0)
Barbiturates	4.4 (18)	4.4 (18)
Buprenorphine	Not performed	4.7 (19)
Cocaine	3.2 (13)	3.2 (13)
Ethanol	1.5 (6)	Not performed
Amphetamine	1.0 (4)	1.0 (4)
Propoxyphene	1.0 (4)	0.7 (3)
6-MAM	Not performed	0.2 (1)
PCP	0.2 (1)	0.0 (0)

[a]Percentage based on a total of 407 patients. [b]Opioid confirmation was performed on all specimens regardless of screen result. Due to technical performance of opioid screen, screen result may be negative when opioid present. Patients may test positive for more than one group of opioids, therefore, the absolute numbers are not additive. THC, tetrahydrocannabinol; MDMA, methylenedioxymethamphetamine; 6-MAM, 6-monoacetylmorphine; PCP, phencyclidine.

and ~15% were positive for benzodiazepines and fentanyl. Less than 10% of patients were positive for amphetamine, barbiturates, buprenorphine, cocaine, ethanol, 6-MAM, MDMA, PCP, propoxyphene, THC and tramadol. We found that 10% of patients had no drugs detected in their specimen.

False positive screening results with immunoassays can be obtained due to cross-reactivity with structurally related drugs outside the target class. The 19 positive screening results for MDMA and one positive screening result for PCP could not be confirmed with gas chromatography/mass spectrometry (Table 2). The false positive results were due primarily to over-the-counter medications such as pseudoephedrine. Twenty-five percent (1 out of 4) of screening results for propoxyphene were falsely positive as were 13% (9 out of 68) of benzodiazepines. False positive results were infrequently seen with methadone and opioids. No other drugs produced false positive screens during the examination of 3 months of data.

The number of false negative opioid screening results was apparent because, unlike the testing protocol for other drugs, opioid confirmations were performed on all patients regardless of screen results. One patient who had a positive confirmatory test for morphine and/or codeine had a negative screen, while sixty-two patients who had a positive confirmatory test for oxycodone and/or oxymorphone had a negative screen result (Table 2).

The confirmed positive test results were compared to the list of prescribed medications in the electronic medical record for all patients (Tables 3 and 4). Overall, ~85% of patients with a prescription for a particular medication tested positive for that medication (Table 3). The compliance rate based on an individual drug was >80%, with the exception of tramadol which was 74%. Nine patients (2.3%) tested negative, even though they were prescribed more than one drug. Tramadol, morphine and codeine, and fentanyl showed the highest non-compliance rate or potential for drug diversion with 26.3%, 16.1% and 14.5% of patients not taking the prescribed medication, respectively.

Of all patients tested, 28.7% tested positive for at least one drug or medication they were not prescribed (i.e., potential drug abuse) (Table 4). The potential abuse rate for morphine and codeine, THC and benzodiazepines was 5%–10%. Twenty-eight patients (9.3%) were potentially abusing more than one drug. Eleven patients (2.7%) had more than one incident in which non-prescribed medications were detected in their urine.

Discussion

While the turnaround time for results for patients on chronic therapy is not as critical as for patients in the emergency department, it is important to have the results in a timely manner (i.e., within 1 week). Clinicians may be waiting for results to determine patient acceptance into the program or to decide whether to refill a prescription. As encountered in our laboratory, turnaround time may be longer than a week due to the need to send the specimen for testing at a reference laboratory. If turnaround time is unacceptable to clinicians, the clinical laboratory should consider performing some or all testing in-house.

We observed an average annual increase of 34% in yearly test volumes between 2005 and 2008. We can

Table 3 Percentage of patients taking prescribed medications.

Drug (number of prescriptions)	% patients with prescription for a medication that appropriately shows up in drug test[b]	% patients with prescription for a medication missing in drug test
All drugs (n=387)	85.3	14.7
Oxycodone, oxymorphone (n=254)	93.3	6.7
Morphine, codeine (n=87)	83.9	16.1
Hydromorphone, hydrocodone (n=69)	88.4	11.6
Methadone (n=85)	95.3	4.7
Benzodiazepines (n=100)	91.0	9.0
Fentanyl (n=55)	85.5	14.5
THC (in the form of marinol) (n=5)	100.0	N/A
Tramadol (n=19)	73.7	26.3
MDMA[a] (n=0)	N/A	N/A
Barbiturate (n=9)	88.9	11.1
Buprenorphine[a] (n=0)	N/A	N/A
Cocaine[a] (n=0)	N/A	N/A
Ethanol[a] (n=0)	N/A	N/A
Amphetamine[a] (n=0)	N/A	N/A
Propoxyphene (n=3)	100.0	N/A
6-MAM[a] (n=0)	N/A	N/A
PCP[a] (n=0)	N/A	N/A

[a]Drugs not prescribed by physicians at the Pain Clinic. [b]As described in the Materials and methods section, confirmed negative tests are seen in both compliant and non-compliant patients. THC, tetrahydrocannabinol; MDMA, methylenedioxymethamphetamine; 6-MAM, 6-monoacetylmorphine; PCP, phencyclidine.

attribute the increase in test volume to multiple factors over the past several years, including the published guidelines, data from literature cited in this study and fear of prescribing narcotics to addicts or patients abusing the system. Primary care and internal medicine clinicians are realizing the importance of screening patients as evidenced by the increase in the number of specimens received from areas other than the pain clinic. Furthermore, our hospital is in the process of implementing guidelines for monitoring patients on chronic pain therapy which will include clinical laboratory testing.

Table 4 Patients testing positive for a drug or medication without a prescription.

Drug	% patients testing positive for medications without prescription (n=407)
All drugs	28.7
Oxycodone, oxymorphone	3.2
Morphine, codeine	6.1
Hydromorphone, hydrocodone	4.2
Methadone	2.5
Benzodiazepines	5.9
Fentanyl	1.5
THC[a]	4.9
Tramadol	1.5
MDMA	0.0
Barbiturate	2.7
Buprenorphine[a]	3.2
Cocaine[a]	3.2
Ethanol[a]	1.5
Amphetamine[a]	1.7
Propoxyphene	0.0
6-MAM[a]	0.2
PCP[a]	0

[a]Drugs not prescribed by physicians at the Pain Clinic. THC, tetrahydrocannabinol; MDMA, methylenedioxymethamphetamine; 6-MAM, 6-monoacetylmorphine; PCP, phencyclidine.

From the additional testing in patients on chronic pain therapy, clinical laboratories can expect an increase in cost related to the increase in the number of positive results for some drugs or classes of drugs. Different screening and confirmatory methods must be performed to cover the breadth of the chronic pain panel. For example, five different immunoassays are currently necessary to screen for morphine, heroin, tramadol, fentanyl and buprenorphine because there is a lack of cross-reactivity in the current assays as well as separate confirmatory tests. This testing increases the cost considerably. For laboratories that would like to perform the testing in-house, or are examining cost saving opportunities, the percentage of positive drug test results are useful for determining testing logistics. Virtually no patients were positive for 6-MAM (which only confirms recent heroin use within the past 6–8 h), MDMA, and PCP. To decrease cost, testing for 6-MAM, MDMA, and PCP may not be necessary or could be limited to only those patients with a high likelihood of recent use. However, differences in patterns in drug use across the US should be considered. Confirmatory testing is typically more expensive than screening and more difficult to implement. Utilizing a low cost but sensitive screening test, if available, would also decrease the cost of testing. As evidenced by the number of false negative results, the opioid screen used by our reference laboratory is not sensitive to oxycodone or oxymorphone. An immunoassay screen specific for oxycodone is now available and could obviate the need for and cost of opiate confirmations in all patient specimens. In

addition, confirmation of all results may not be necessary if the screening results are consistent with the patient's medications.

Our clinical laboratory frequently receives requests from physicians, particularly those who lack expertise in pain management, to help with result interpretation. This may be related to the increase in the number of positive results and the fact that patient management is closely tied to these test results. Other laboratories may also expect an increase in the number of inquiries and should be prepared to educate technical and medical staff and help with interpretation of test results. An important aspect of result interpretation is to understand that the cross-reactivity (i.e., the amount of drug required to trigger a positive result) depends upon which drug in the class is present and the immunoassay technique utilized by the laboratory. The results obtained with the EMIT assay, used by our reference laboratory, may not be the same as those obtained by laboratories using different assay methods. Laboratory directors should understand the performance of their particular assays and communicate this to the clinicians.

We found that ~15% of patients were not taking their prescribed medication or potentially diverting it, and ~30% were potentially abusing drugs. According to the medical records, suspicion for diversion was low. Tramadol showed the highest rate of non-compliance. However, this result may be skewed due to the low number of patients. In addition, drug use is specific by region; our results may not be applicable to other populations of chronic pain patients. The high potential abuse rate for benzodiazepines and opioids may be due to high prescription frequency and wide availability of these drugs. Similar to the general population, patients in chronic pain commonly abuse THC. The abuse rate for illicit drugs such as heroin (as reflected by 6-MAM), amphetamines, cocaine, PCP and MDMA was relatively low in this patient population and is consistent with our suggestion to eliminate screening for these drugs. Overall, our findings suggest that a targeted and cost-effective comprehensive panel to detect compliance, diversion and/or use of undisclosed substances is warranted in chronic pain patients regardless of their medication history.

The addition of testing from patients on chronic pain therapy has increased the complexity of our test menu and has had a significant technical and clinical impact on our laboratory. We are in the process of implementing some of the suggestions mentioned above. To aid with test interpretation, we are preparing guidelines that will indicate the drugs that can or cannot be detected by each immunoassay, and the criteria for confirmatory testing. In addition, we are limiting the test panel, implementing an oxycodone specific immunoassay screen and performing testing in-house to optimize the testing algorithm and reduce the financial burden.

Conflicts of interest

The authors have no conflicts of interest.

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