

Retrospective Evaluation

Illicit Drug Use Correlates with Negative Urine Drug Test Results for Prescribed Hydrocodone, Oxycodone, and Morphine

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Background: A number of studies indicate that 10.8% - 34% of patients with chronic pain use illicit drugs. One hypothesis for this occurrence is that some patients may be supplementing their prescription medications with illicit drugs.

Objective: The primary purpose of this retrospective data analysis was to test the hypothesis that people whose urine specimens are positive for the medications that have been listed as being prescribed to them are positive for fewer illicit substances than those whose specimens were negative for their prescribed medications. The secondary purpose of the study was to correlate the use of illicit drugs and the amount of prescribed medications excreted in urine.

Study Design: A retrospective study of the incidence of patients using illicit drugs versus their consistency with reported medications.

Methods: Using urine specimens from a cohort of nearly 400,000 patients whose identities had been redacted, and who were being treated for chronic pain with opioid therapy, this study was performed to correlate the patients' positivity with their prescribed medication to the prevalence of illicit substance use. A secondary study was conducted to correlate the amount of prescribed medication excreted in urine (measured in ng/mL) with the incidence of illicit drug use. The specific prescription medications analyzed were hydrocodone, morphine, and oxycodone.

Results: Specimens defined as negative for prescribed hydrocodone (27.3%), morphine (11.5%) or oxycodone (19%) were more likely to contain illicit drugs than those found to be positive for the prescribed medication. The illicit drug prevalence among the inconsistent specimens was 15.3% for hydrocodone, 23.8% for morphine, and 24.4% for oxycodone. The secondary study showed no statistically significant difference in the excretion level of prescribed medication between those patients using and not using illicit drugs.

Limitations: The study is limited in that no data was obtained to determine the causal relationships of illicit drug use.

Conclusions: This work supports the hypothesis that people who are positive for their prescribed medications use fewer illicit drugs than those who do not take their medications. It may be beneficial for physicians to test more thoroughly for illicit drugs when patients' drug tests are negative for their prescribed medications.

Key words: Patients with pain, illicit drug use, hydrocodone, morphine, oxycodone.:

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A number of studies indicate that 10.8% - 34% of the patients with chronic pain use illicit substances (1-9). Urine drug testing is commonly used by pain clinicians as a means of monitoring their patients on chronic opioid therapy (10-15). Because opioid medications are scheduled, and because patients treated for pain commonly take a number of medications which place them at risk, it is important for treating clinicians to know as much as they can about whether a patient is taking their medications, unprescribed medications, or illicit substances.

At the most obvious and basic level, this is often accomplished by simply asking if the patient is following the prescribed medication regimen. One way to cross-check this is to conduct pill counts, that is, have the patient bring the medication containers to the office at the time of the visit and literally count the pills in the containers. This kind of interaction is not particularly comfortable for either the physician or the patient because it brings into question the level of trust that has been established. Pill counts may be conducted following behavior that has caused the physician to become concerned that the patient is either using too much, too little, or none at all of the prescribed medication.

One means of augmenting both patients' reports of medication usage and pill counts, if they have been conducted, is the use of urine drug testing, which is a recommended and recognized component of treating the pain population (16-18).

Urine drug testing provides objective and accurate data about the presence and concentration of medications and other substances that have been excreted by a patient in urine at a given moment in time (16-19). Urine drug testing is limited to this information and does not provide accurate data about the dosage a patient is taking (12,13). This is because the amount of a substance excreted in urine is a function of many factors that extend beyond the amount or dosage that the patient has taken. The urine drug concentration can be affected by the timing of the dose in relation to the time when the specimen was acquired, the pharmacogenomic makeup of the patient, the age of the patient, gender, and renal function as well (20,21).

It has been shown in one small cohort that 23 out of 100 urine specimens from patients in this population were positive for illicit substances (2). A second study of 200 patients in this population, who were prescribed hydrocodone or methadone, showed that 22%-24% of the patients had used illicit drugs (3). These studies

indicated that patients were not positive for their prescribed medications and that they used illicit substances. However, the numbers were not great enough to make any definitive judgment about whether those patients who take opioids other than the ones prescribed are more likely to use illicit substances.

The primary purpose of this study was to test the hypothesis that people in the pain population whose urine specimens are positive for the medications that have been listed as being prescribed to them are positive for fewer illicit substances than those whose specimens were negative for prescribed medications.

The secondary purpose of the study was to utilize a large database of urine drug tests from Millennium Laboratories covering a nearly three-year period (March 2008 through September 2010) to perform a quantitative study to correlate the use of illicit substances and the concentrations of excreted prescribed medications in urine. The identities of those in the database were redacted.

METHODS

This research was approved by the Aspire Institutional Review Board, Santee, CA. All specimens were tested by liquid chromatography-tandem mass spectrometry (LC-MS/MS) at Millennium Laboratories, San Diego, CA. The analytical methods used have been previously described (19,22-24). As this study was retrospective in nature, the treatment of patients was not affected. No outside funding was provided for this study.

The study cohort was composed of urine excretion data from almost 400,000 specimens from patients treated with opioids for chronic pain. The patient medication lists were sorted so that only patients on monoopioid therapy of the specific medications hydrocodone, morphine, and oxycodone were used in the analysis.

If a patient specimen was not tested for carboxy-THC (marijuana metabolite), benzoylecgonine (cocaine metabolite), methamphetamine, phencyclidine (PCP), MDMA (ecstasy), or 6-acetylmorphine (heroin metabolite), that patient entry was deleted in the analysis. The sorted data resulted in the following groups: 5,750 specimens listed as prescribed hydrocodone, 3,152 specimens listed as prescribed morphine, and 12,913 specimens listed as prescribed oxycodone. The cutoff concentrations used for the medications and illicit substances analyzed in this study are identified in Table 1. Statistical analysis was conducted using SAS® Version 9.1, (SAS Institute Inc., Cary, NC).

For the first part of the study, medications and il-

licit drugs were qualified as being present or absent according to the concentration quantified by LC-MS/MS. Four groups were separated: 1) those that tested negative for the medication and negative for illicit drugs; 2) those that tested negative for the medication and positive for illicit drugs; 3) those that tested positive for the medication and negative for illicit drugs; and 4) those that tested positive for the medication and positive for illicit drugs. The presence of medication and/or illicit drugs for each of the 3 opioid medications was tabulated. This procedure was followed by Chi-squared analysis and identification of the *P* value.

In the second part of the study, the use of illicit drugs was correlated with the quantitative excretion of each of the 3 medications. Any of the specimens containing illicit drugs that were present above their respective cutoff concentrations were qualified as positive results. The mean concentration of opioid medication was calculated for the specimens where illicit drugs were not observed and for the specimens where illicit drugs were observed. Finally, the significance of the difference of the mean concentrations was determined.

RESULTS

For all 3 prescribed medications—hydrocodone, morphine, and oxycodone—the correlation was strongest for illicit drug use in specimens where the prescribed medication was not observed.

Table 2 lists the correlation between the presence of hydrocodone and illicit drug use. Of the 5,750 patients listed as being prescribed hydrocodone, 1,567 specimens were negative for the presence of this medication. This represented an absence rate of 27.3% for hydrocodone. Of those, 15.3% were taking illicit drugs compared to 12.8% of the patients who were positive for their prescribed medication (*P* = 0.0139).

Table 3 lists the correlation between those specimens positive for prescribed morphine and illicit drug use. Of the 3,152 patients listed as being prescribed

morphine, 362 specimens were negative for the presence of this medication. This represented an absence rate of 11.5% for morphine. Of the specimens from patients negative for their prescribed morphine medication, 23.8% were found to be positive for illicit drugs compared to 13.3% of the specimens from patients that were positive for their prescribed medication (*P* < 0.0001).

Table 4 lists the correlation between positivity for prescribed oxycodone and illicit drug use. Of the 12,913 specimens from patients listed as being prescribed oxycodone, 2,456 specimens were negative for the presence of this medication. This represented an absence rate of 19% for oxycodone. Of specimens from non-adherent patients negative for their prescribed oxycodone, 24.4% were positive for illicit drugs compared to 17.2% of the specimens from patients that were positive for their medication (*P* < 0.0001).

When the amount of excreted prescription medication was measured, no difference was identified in

Table 1. Parent drugs, metabolites, and cutoff levels used in the study.

Analyte	LC-MS/MS Cutoff Level (ng/mL)
Medications	
Hydrocodone	50
Morphine	50
Oxycodone	50
Illicit Drugs	
Carboxy-THC (marijuana)	15
Benzoyllecgonine (cocaine)	50
6-acetylmorphine (heroin)	10
MDMA (ecstasy)	100
Methamphetamine	100
Phencyclidine (PCP)	10

Table 2. Correlation between presence of prescribed hydrocodone and illicit drug use.

Category	No Hydrocodone	Hydrocodone Observed	Total
No Illicit Drugs	1,328 (84.7%)	3,649 (87.2%)	4,977 (86.6%)
Illicit Drugs Observed	239 (15.3%)	534 (12.8%)	773 (13.4%)
Total	1,567	4,183	5,750
Statistics	Chi Square 6.05	P Value 0.0139	

Table 3. Correlation between presence of prescribed morphine and illicit drug use.

Category	No Morphine	Morphine Observed	Total
No Illicit Drugs	276 (76.2%)	2,419 (86.7%)	2,695 (85.5%)
Illicit Drugs Observed	86 (23.8%)	371 (13.3%)	457 (14.5%)
Total	362	2,790	3,152
Statistics	Chi Square 28.2	P Value <0.0001	

Table 4. Correlation between presence of prescribed oxycodone and illicit drug use.

Category	No Oxycodone	Oxycodone Observed	Total
No Illicit Drugs	1,856 (75.6%)	8,662 (82.8%)	10,518 (81.5%)
Illicit Drugs Observed	600 (24.4%)	1,795 (17.2%)	2,395 (18.5%)
Total	2,456	10,457	12,913
Statistics	Chi Square 69.5	P Value <0.0001	

Table 5. Correlation between mean medication excretion concentration and illicit drug use.

Pain Medications	No. Negative Illicit Drug Observations	Mean Excreted Medication Concentration (ng/mL)	No. Positive Illicit Drug Observations	Mean Excreted Medication Concentration (ng/mL)	P Value
Hydrocodone	3,649	2,508	534	2,558	0.85
Morphine	2,419	42,158	371	49,356	0.07
Oxycodone	8,662	22,159	1,795	21,105	0.69

the mean concentration of excreted medication between those patients using illicit drugs and those patients not using illicit drugs. This was true for each of the 3 medications. Table 4 lists the correlation between mean medication excretion and illicit drug use. For hydrocodone, the mean excretion value for those patients not taking illicit drugs was 2,508 ng/mL. For those patients who were found to be taking illicit drugs, the mean excretion value was 2,558 ng/mL. The difference between the 2 groups was not statistically significant ($P = 0.85$). For morphine, the mean excretion value for those patients not taking illicit drugs was 42,158 ng/mL. For those patients taking illicit drugs, the mean excretion value was 49,356 ng/mL. This was also not statistically significant ($P = 0.07$). Finally, for oxycodone, those patients not taking illicit drugs had a mean excretion value for that drug of 22,159 ng/mL, whereas the patients taking illicit drugs had a mean excretion value of 21,105 ng/mL. This difference was also not statistically significant ($P = 0.69$).

DISCUSSION

The use of illicit drugs in combination with opioid medications places patients at significant risk (5). In previous work, the authors of this study established that illicit substance use among the population of patients with pain can be reduced by frequent drug testing (8). In addition, urine drug testing has been shown to be cost effective (25). Doctors face the questions of which patients to test, what to test for, and how often to test.

The data from the present study indicate that patients whose urine specimens were positive for the medications listed as having been prescribed to them were less likely to be positive for illicit substances than patients whose urine specimens were negative for those listed prescribed medications. Those who test positive for their prescribed medications require less frequent testing for illicit substances than those whose test results are negative for prescribed medications.

An attempt to see if there was a correlation be-

tween the concentration of prescribed medication present and the presence of illicit substances did not show any relationship. In other words, specimens with greater concentrations of the excreted prescribed opioids did not correlate with less presence of illicit substances.

A limitation of this study is that the search for illicit substances was not comprehensive. That is, not all possible illicit drugs were determined by the analytical assays presented in this paper.

CONCLUSIONS

The data presented in this retrospective study indicate that patients who are positive on urine drug analysis for prescribed hydrocodone, morphine, or oxycodone are less likely to take illicit substances than those patients whose specimens were negative for their prescribed medications. It may be beneficial for physicians to test more thoroughly for illicit substances when patients' urine drug tests are negative for their prescribed medications.

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