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Diagnostic Accuracy Report

Comparative Evaluation of the Accuracy of Benzodiazepine Testing in Chronic Pain Patients Utilizing Immunoassay with Liquid Chromatography Tandem Mass Spectrometry (LC/MS/MS) of Urine Drug Testing

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Background: Eradicating or appreciably limiting controlled prescription drug abuse, such as opioids and benzodiazepines, continues to be a challenge for clinicians, while providing needed, proper treatment. Detection of misuse and abuse is facilitated with urine drug testing (UDT). However, there are those who dispute UDT's diagnostic accuracy when done in the office (immunoassay) and claim that laboratory confirmation using liquid chromatography tandem mass spectrometry (LC/MS/MS) is required in each and every examination.

Study Design: A diagnostic accuracy study of UDT.

Study Setting: The study was conducted in a tertiary referral center and interventional pain management practice in the United States.

Objective: Comparing UDT results of in-office immunoassay testing (the index test) with LC/MS/MS (the reference test).

Methods: A total of 1,000 consecutive patients were recruited to be participants. Along with demographic information, a urine sample was obtained from them. A nurse conducted the immunoassay testing at the interventional pain management practice location; a laboratory conducted the LC/MS/MS.

All index test results were compared with the reference test results. The index test's efficiency (agreement) was calculated as were calculations for sensitivity, specificity, false-positive, and false-negative rates.

Results: Approximately 36% of the specimens required confirmation. The index test's efficiency for prescribed benzodiazepines was 78.4%. Reference testing improved accuracy to 83.2%, a 19.6% increase, and 8.9% of participants were found to be taking non-prescribed benzodiazepines. The index test's false-positive rate for benzodiazepines use was 10.5% in patients receiving benzodiazepines.

Limitations: This study was limited by its single-site location, its use of a single type of point of care (POC) kit, and reference testing being conducted by a single laboratory, as well as technical sponsorship.

Conclusion: Clinicians should feel comfortable conducting in-office UDT immunoassay testing. The present study shows that it is reliable, expedient, and fiscally sound for all involved. In-office immunoassay testing compares favorably with laboratory testing for benzodiazepines, offering both high specificity and agreement. However, clinicians should be vigilant and wary when interpreting results, weighing all factors involved in their decision.

Key words: Controlled substances, benzodiazepines, opioids, illicit drugs, abuse, liquid chromatography tandem mass spectrometry, immunoassay, urine drug testing

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The treatment of chronic pain with escalating controlled substance use and abuse, and the nonmedical use of prescription drugs have been topics of intense focus and debate (1). The controlled substances often prescribed for chronic noncancer pain include not only opioids, but also various other drugs including benzodiazepines. Benzodiazepines have been shown to be as abused as opioids; they have also resulted in similar emergency department visits (2-15). The present state of affairs is based on prescriptions for chronic noncancer pain; subjective complaints of pain; prevalence of psychologically-specific anxiety and sleep disorders in chronic pain patients; recommendations from federal, state, and local governments; professional associations; massive sales promotion activities from the pharmaceutical companies; physicians promoting opioid therapy with comorbid disorders; accreditation agencies promoting pain management in conjunction with a biopsychosocial approach, which involves psychological management including psychotherapeutic drug therapy; and finally the public-at-large expecting pain relief and relief of all symptoms at any cost, rather than on scientific data on efficacy and safety (1,7-18). The results from the 2009 National Survey on Drug Use and Health illustrated increasing use of benzodiazepines (1,7). Further, national estimates of drug-related emergency department visits (8) also showed increasing visits related to benzodiazepines at a rate similar to opioids. Consequently, benzodiazepines are considered the most frequently prescribed sedatives and hypnotic drugs with increasing evidence of overuse, abuse, and dependence (19,20). Benzodiazepine abuse is associated with the abuse of alcohol and other psychoactive substances, along with widespread use among heroin addicts treated with methadone (21-23). Benzodiazepines have been described as part of the methadone program to alleviate some of the withdrawal symptoms of treated heroin addicts such as insomnia, nausea, anxiety, and depression.

The prevalence of chronic pain and its associated disability continue to increase (24-26). Similar to the extensive therapeutic use of opioids and benzodiazepines, along with associated abuse and dependence, a multitude of other techniques, including interventional pain management techniques, also have been escalating (27-30). Further, the psychological issues associated with chronic pain, specifically, generalized anxiety disorder, have also been shown to be present in greater than 50% of patients (31-35). Following a biopsychosocial perspective in management, instead of utilizing behavioral therapy, practitioners are increasingly utilizing benzodiazepines to manage anxiety, and even occasionally depression, as well as all other types of symptoms, including muscle spasm.

The challenge is to eliminate or significantly curtail abuse of controlled prescription drugs while still assuring the proper treatment of those patients with evident indications. Adherence monitoring, including urine drug testing (UDT), has been shown to be a useful approach to assist in identifying and/or predicting patterns of drug use, compliance, misuse, and abuse (36-38). UDT provides relatively good specificity, sensitivity, ease of administration, and cost for various drugs including benzodiazepines (6,19,36-49). However, controversies also exist 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 application in chronic pain management settings. Further, additional issues also exist related to excessive use, misuse, abuse, and financial incentives (36-38,47-57). UDT is performed to detect the presence of prescribed medications (i.e., compliance testing) and to identify substances that are not expected to be present in the urine, such as non-prescription or illicit drugs (i.e., forensic testing). The most commonly used Current Procedural Terminology (CPT) codes for UDT, 80101 and 80102, showed 343% and 364% increases from 2004 to 2007 and an increase in allowed charges of 452% and 387%; the total allowed charges exceeded $50 million in 2007 (57). The abuses related to the utilization of UDT, its value and validity, and exploding costs, has led the Centers for Medicare and Medicaid (CMS) administration to impose new regulations for UDT reimbursement (47-57).

Consequently, the pain physician is confused by the available options, indications, and medical necessity of UDT. Recently, Christo et al (37) illustrated an algorithmic approach to UDT. Even so, debate continues regarding the validity of in-office UDT of chronic pain patients by immunoassay methodology that has not been validated with liquid chromatography tandem mass spectrometry (LC/MS/MS). Recently, Manchikanti et al (38) published a comparative evaluation of the accuracy of immunoassay with LC/MS/MS of UDT of opioids and the use of drugs in chronic pain patients. Overall results showed that confirmation was required in 32.9% of the specimens, without taking into consideration a history and evaluation for opioids and illicit drugs. Agreement for prescribed opioids was high

with the index test (80.4%), whereas the reference test for opioids improved accuracy by 8.9% from 80.4% to 89.3%. However, positive results with the reference test were also the same as the index test with a positive rate of 79.7%. This evaluation also showed that non-prescribed opioids were used by 5.3% of patients. The index test provided false-positive results for non-opioid use in 44%, or 83 of 120 patients. Test efficiency or agreement was present in over 90% for all opioids and for illicit drugs, approaching 99.4%; ranging from a low of 90% for oxycodone, to 98.7% for methadone, and an even higher agreement of over 97% for all illicit drugs tested (marijuana, cocaine, methamphetamines, and amphetamines). The authors concluded that UDT with immunoassay in an office setting is appropriate, convenient, and cost-effective. However, they caution that due to variable sensitivity, clinicians would be well-advised to take a cautious approach when interpreting the results, in conjunction with other compliance monitoring measures.

Thus, despite the recent report, due to multiple methodological issues, an in-office immunoassay confirmed by an independent laboratory is commonly regarded as the best and most sensitive UDT, even at the expense of escalating costs. Other issues involved are the knowledge of the physician who interprets the drug screening, including knowledge about opioid and benzodiazepines metabolites, appropriate testing methods in an office setting, and the cost involved (37,38,50,53,54,56,57).

At present, the marketing efforts of UDT manufacturers and physicians who receive substantial income from UDT continue to market the value and validity of laboratory testing and describe it as the only way to monitor compliance consistently despite escalating costs (37,38,47,50-56). However, others recommend in-office testing for the reasons of convenience and cost effectiveness (37,38). While the issues have been well studied for prescription opioids, there is a paucity of literature concerning prescription benzodiazepines.

Benzodiazepines are structurally similar to one another, and it has been described that the most convenient screening methods for UDT for benzodiazepines are based on immunoassay, and only inappropriate results need to be confirmed, usually using gas chromatography, or liquid chromatography coupled with mass spectometry (58-60). However, these methods are not suitable for quantification in some biological samples due to the presence of their different metabolites and/or other substances in the matrix with similar properties (19,58-60). Thus, multiple techniques have been developed to assess levels of benzodiazepines (19,61-64).

This diagnostic accuracy study has been undertaken to evaluate the accuracy of immunoassay compared to LC/MS/MS of UDT. The results of opioid and benzodiazepine testing, as well as illicit drug use in chronic pain patients and their correlations, have been published in a previous report (38). This report describes comparative evaluation of the accuracy of benzodiazepines.

Methods

The study was undertaken in an interventional pain management practice, a tertiary referral center, in the United States. The protocol was approved by the Institutional Review Board (IRB) of the Ambulatory Surgery Center and it has a clinical trial registration of NCT01052155. Appropriate precautions were taken to protect the privacy and identity of patients evaluated from this study in accordance with current Health Insurance Portability and Accountability Act (HIPAA) regulations.

The protocol has been described in a previous publication (36). The study was performed utilizing the Standards for Reporting of Diagnostic Accuracy Studies (STARD) established for reporting guidelines for diagnostic accuracy studies to improve the quality of reporting (65-67). The results of opioid and illicit drug use have been published (38).

Objective

The objective of this study was to compare results of UDT of immunoassay in-office testing (index test) with LC/MS/MS (reference test).

Proposed Hypothesis

It is proposed that there is no significant difference of clinical importance between point of care (POC) drug testing (index test) and laboratory drug testing (reference test).

Investigational Methodology

The investigational methodology followed the STARD checklist (65). All specimens were tested with immunoassay (index test) and LC/MS/MS (reference test).

Participants and Recruitment

Consecutive series of patients presenting for interventional pain management were recruited in a prospective manner.

Inclusion and Exclusion Criteria

Consecutive patients in chronic pain management were included. There were no exclusion criteria.

Test Methods

The index test was in-house POC office drug testing with immunoassay; the reference standard was LC/MS/MS.

The laboratory test (reference test) was performed by Millennium Laboratories, which holds certificates for moderate and high complexity testing.

Screening Evaluation

All consecutive patients participating in the urine drug assessments diagnostic accuracy study were provided with a verbal explanation of the study. IRB-approved written informed consent to participate in the study was obtained.

Demographic details including date of birth, sex, weight, height, and drug profiles (which included a list of all prescription and over-the-counter drugs, as well as all other drugs or substances they were taking) were obtained.

Treatment Number Assignment

Participants were consecutively assigned a number.

Urine Sample

Urine and all other appropriate information were collected by a nurse participating in the study and provided to the study coordinator. POC testing was performed by a different nurse who was unaware of the patient's name, drug intake, etc. Drug testing was performed for opioids, benzodiazepines, and illicit drugs.

Laboratory Assessment

After immunoassay, the samples were sent to a laboratory for LC/MS/MS without any identifying information or results of the index text.

Definition and Rationale

The definition and rationale for the units, cutoffs, and categories of the results of the index test and the reference standard have been described (36,38).

Personnel

Six nurses, determined to be a sufficient number, received training to conduct and read the index test. The reference test was conducted by trained, certified professionals at the laboratory.

Blinding

The personnel performing and reading the index tests and reference tests were blinded (masked) to the results of the other tests as well as patient demographics.

Statistical Methods

Sample Size

Sample size calculation was carried out for our primary outcome (accuracy of the POC drug test in screening for opioids, benzodiazepines, and illicit drugs) according to the previously published method (68), and previous results of drug abuse and illicit drug use by patients referred to clinics (2,9-11). The details are provided in previous publications (36,38). The sample size was calculated at 811 with a planned enrollment of 1,000 patients to be tested.

Analysis

Statistical analysis was performed using SPSS 9.01 (SPSS, Inc., Chicago IL, USA). A *P* value below 0.05 was considered statistically significant.

Results of the index test were compared to the reference test in all patients. The sensitivity, specificity, false-positive and false-negative rates, and index test efficiency (agreement) were calculated.

Results

Flow Diagram

Figure 1 illustrates the patient flow diagram per STARD for benzodiazepines.

Participants

The study lasted from March 1, 2010, through June 30, 2010, with enrollment of consecutive patients.

Demographic Characteristics

The demographic characteristics of the study population are illustrated in Table 1.

Validity and Test Reproducibility

One hundred specimens without identification or demographic data were tested for validity of the reference test. This showed perfect correlation.

Numbers Analyzed

The numbers analyzed are illustrated in Fig. 1.

Time Intervals

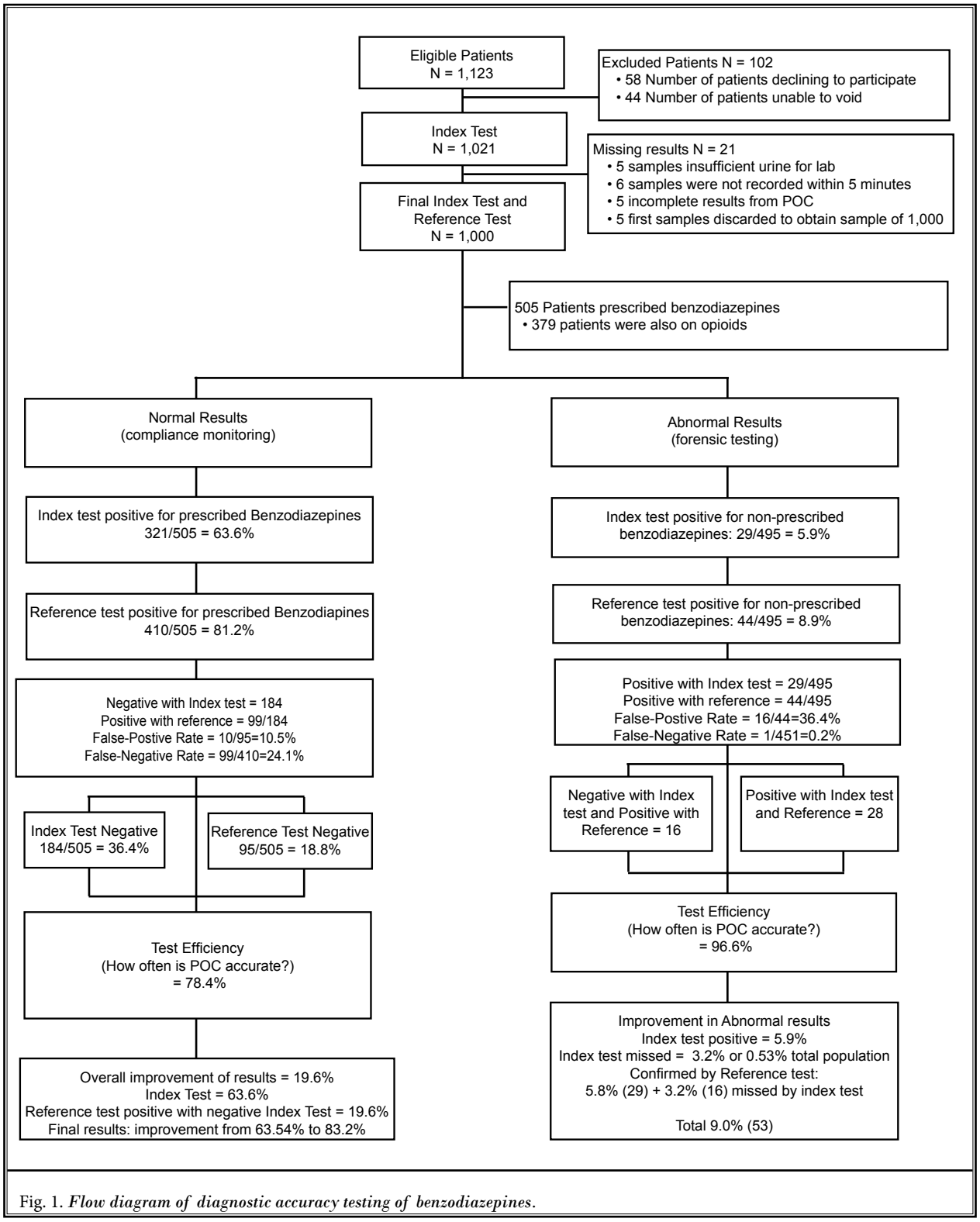

Fig. 1. *Flow diagram of diagnostic accuracy testing of benzodiazepines.*

Table 1. *Demographic characteristics of patients undergoing urine drug testing.*

		Number
Gender	Male	37% (370)
	Female	63% (630)
Age (Years)	Mean ± SD	51 ± 12.6
Height		66.5 ± 4.2
Weight		184.1 ± 51.5
Insurance	Medicare	20.7% (207)
	Medicaid & Medicare	15.3% (153%)
	Medicare & Third Party	11.0% (110)
	Medicaid	25.2% (252)
	Self Pay	1.9 (19)
	Third Party	22.5% (225)
	Workers' Compensation	3.4 (34)
State	Kentucky	82.9% (829)
	Other States (IL, TN, MO, IN)	17.1% (171)

The index test and reference test were performed on the same sample. The time interval for transporting the sample to the lab and performance of the test is estimated to have been 72 hours.

Distribution Characteristics

The distribution of severity of disease is not applicable.

Cross Tabulation of the Results

A cross tabulation of the results of the index test and the reference test was performed.

Adverse Events

No adverse events occurred while performing the index test or reference test.

Estimates

The estimated diagnostic accuracy and comparison were evaluated for all patients for each benzodiazepine prescribed and for illicit drugs.

Results of Accuracy of Benzodiazepine Testing

Table 2 illustrates a summary of the diagnostic accuracy of benzodiazepines with detailed data from the index test and the reference test.

Discussion

The comparative evaluation of the accuracy of UDT for benzodiazepine detection in chronic pain patients utilizing both immunoassay and LC/MS/MS showed significant agreement for benzodiazepines similar to opioids and illicit drugs. This assessment showed test efficiency of 87.4% when all patients were assessed compared to 78.4% in patients with prescribed benzodiazepines, and 96.6% in patients without prescribed benzodiazepines. Positive predictive value, which shows how often a positive office test is correct, was 96.9%. Specificity was high, being 98% when all patients were assessed, 89.5% when only patients with prescribed benzodiazepines were considered, and 99.8% for patients without prescribed benzodiazepines. However, sensitivity was lower compared to specificity with 75.9% of the patients with prescribed benzodiazepines and 63.6% of the patients without prescribed benzodiazepines. The false-positive rates varied from 0.2% in patients without prescribed benzodiazepines to 2% when all patients were assessed, and 10.5% in patients with prescribed benzodiazepines. However, false-negative rates with patients being misdiagnosed as negative, when in fact they were positive, was relatively high, 24.1% in patients with prescribed benzodiazepines and 36.4% in patients without prescribed benzodiazepines. Consequently, one can miss a significant proportion of patients without prescribed benzodiazepines; however, to obtain this result all 1,000 specimens had to be sent for confirmation. In contrast, only 29 of 495 patients not on benzodiazepines tested positive for benzodiazepines with POC testing. Thus, when 29 of these specimens were confirmed by LC/MS/MS, only 16 were positive, thus improving the diagnostic accuracy only slightly.

In patients taking benzodiazepines, the index test was positive in 63.6% of the patients, whereas the reference test was positive for prescribed benzodiazepines in 81.2%, a wider difference than opioids, where it was shown to be equal at approximately 80%. It appears that the reference test is equally accurate for opioids and benzodiazepines; however, the index test is positive in a lower proportion of patients. When all the index test negative specimens (184 of 505, or 36.4%) were confirmed by the reference test, the overall results improved by 19.6%, thus improving the final results from 63.6% to 83.2%, a number which is 2 percentage points higher than straightforward reference test results. Thus, confirming only the negative specimens will improve diagnostic accuracy bet-

Table 2. *Summary of diagnostic accuracy of POC vs LC/MS/MS – benzodiazepines.*

		All patients (1000)			Patients with Prescribed Benzodiazepines (505)			Patients without Prescribed Benzodiazepines (495)		
		Reference Test (LC/MS/MS)			Reference Test (LC/MS/MS)			Reference Test (LC/MS/MS)		
		Positive	Negative	Totals	Positive	Negative	Totals	Positive	Negative	Totals
Index Test (POC)	Positive	339	11	350	311	10	321	28	1	29
	Negative	115	535	650	99	85	184	16	450	466
	Totals	454	546	1000	410	95	505	44	451	495
Test Efficiency (How often does the POCT get the right answer?)		87.4%			78.4%			96.6%		
Sensitivity (TP/(TP+FN)		74.7% (70 – 78)			75.9% (71 – 80)			63.6% (47 – 78)		
Specificity (TN/(TN+FP)		98.0% (96 – 98)			89.5% (81 – 94			99.8% (98 – 99)		
False Negative Rate (% of positives that misdiagnosed as negative on POCT)		25.3%			24.1%			36.4%		
False Positive Rate (% of negatives misdiagnosed as positive on POCT)		2%			10.5%			0.2%		
Positive Predictive Value (how often is a positive POCT correct?)		96.9%			96.9%			NA		
Negative Predictive Value (how often is a negative POCT correct?)		82.3%			NA			96.6%		

POCT = point of care testing; TP = true-positive; FN = false-negative; TN = true negative; FP = false-positive

ter than sending all specimens to a lab and depending only on LC/MS/MS results.

Multiple methodological issues are present in UDT, with immunoassays being based on the principle of competitive binding for detecting a particular drug group in a urine sample. In contrast, laboratory-based specific drug identification is sophisticated, but also much more expensive. Thus, laboratory-based specific drug identification is needed to confirm the presence of a given drug and/or to identify drugs that cannot be isolated by a screening test. In addition, the cutoff levels for various drugs detected by urinalysis are also different between immunoassay testing and LC/MS/MS. Consequently, the capability of a particular immunoassay to detect drugs can vary according to both the drug concentration in the urine and the assessed cutoff concentration – with drug levels above cutoff being deemed to be positive. However, almost all immunoassays are subject to cross-reactivity.

POC testing results examined in the present evaluation for benzodiazepines showed overall inappropriate findings in 36.4% of the patients on benzodiazepines (184 of 505), whereas benzodiazepines were present in 29 of the 495 patients, with overall inappropriate results in 213 of 21.3% of the patients. However, false-negative rates were observed in 24.1% of the patients taking prescribed benzodiazepines. The false-positive rate for patients taking prescribed benzodiazepines was 10.5% compared to almost 0% (0.2%) for patients not taking prescribed benzodiazepines. Thus, if all the questionable specimens were sent to the lab, 184 + 29 = 213, the accuracy would be improved for patients who are on benzodiazepines by 19.6%, whereas there was no significant improvement in patients who were not on benzodiazepines.

The present study illustrates results for patients taking prescribed benzodiazepines, with a false-negative rate of 36.4% for the index test and 18.8% for the reference test. The improved diagnostic accuracy with the reference test was 19.6%, rising from 63.6% to 89.2%; all the samples which were tested to be negative by immunoassay were confirmed by LC/MS/MS, with 95 of 184 patients testing positive. In reference to non-prescribed benzodiazepines, 5.9% (29 of 495) tested positive with the index test, with that test missing 8.9% or 44 of 495 patients.

Multiple authors have described the utility and application of UDT for opioids in chronic pain management (9-11,19,36-50,69,70). Nafziger and Bertino (70) described that UDT, when used with an understanding of the principles of pharmacokinetics, pharmacodynamics, and pharmacogenetics of opioids, can be a useful tool in chronic pain management. Thus, clinicians must keep in mind the limitations, purpose, and value of UDT, and the inability to predict patient compliance with the drug dosages used in commercial algorithms. The question which needs to be answered is: How many POC testing samples need to be sent to the lab? Based on our evaluation, it appears that it should be all samples testing negative for prescribed benzodiazepines (184 patients) and positive for non-prescribed benzodiazepines (29 patients), totaling 213. Thus, without consideration of history, these can be reduced based on a patient's admission of abnormal use, and the clinic's policy for controlled substances and illicit drugs. The reductions could range to 2% to 10%, with a repeat of the immunoassay test during the patient's next appointment or at random. A repeat test should be much less expensive compared to sending the test to a lab; generally $25 versus as much as $600. Thus, careful analysis can save substantial amounts of health care dollars, specifically when performed judiciously without repeating during each visit in patients who do test normally, and repeating their tests only once a year and then only repeating in patients who present with abnormal results. One UDT might be more expensive than providing 2 to 3 epidural injections. Routine excessive UDT could result in annual charges as high as $10,000, which is more expensive than managing patients with common opioids and benzodiazepines or appropriately performed therapeutic interventional techniques. However, multiple interventional techniques also have been criticized for escalating use, abuse, and lack of effectiveness (28-31,51,52,71-76). Based on cost-effectiveness, numerous guidelines have been developed, which are curbing chronic pain management therapy in the era of increasing pain, including interventional techniques and surgery based on evidence-based medicine and comparative effectiveness research (26,51,52,77-100). Thus, appropriate use of immunoassay will be cost-effective with provision of appropriate care.

The present study can be criticized for limitations, which include a single site study utilizing a single POC kit and a single laboratory, as well as technical sponsorship. A multicenter study could be performed utilizing various manufacturers and different kits, etc.; however, this might provide irregular results. Consequently, as an initial diagnostic accuracy study, the present study is appropriate. Millennium Laboratories provided urine drug kits, laboratory evaluation at no cost, and expenses for employees for collecting the samples, transporting them, data entry, and analysis. However, they had no influence or interference after the protocol was designed. Further, the authors of the manuscript received no remuneration. Thus, we believe the results are valid.

Further, the results of this study illustrate practice patterns in an interventional pain management practice, rather than results generalizable to either all interventional pain medicine settings or primary care settings.

Conclusion

UDT with immunoassay in an office setting is an appropriate, convenient, and cost-effective test providing rapid results for evaluating opioid compliance. Compared with laboratory testing LC/MS/MS for opioids and illicit drugs, benzodiazepine immunoassay in-office testing had high specificity and agreement, but variable sensitivity.

However, in patients with abnormal results, results are not dependable and might have to be confirmed either by a repeat test, proper history, or confirmation by LC/MS/MS.

Disclosures

Author Contributions: Dr. Manchikanti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Manchikanti, Malla, and Wargo designed the study protocol. Vidyasagar Pampati, MSc, was in charge of data entry, storage, and analysis. Dr. Manchikanti managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. All other authors provided revision for intellectual content and final approval of the manuscript.

Conflict of Interest Disclosures: All authors have no conflicts of interest to report. None of the authors of the manuscript received any remuneration. Further, the authors have not received any reimbursement or honorarium in any other manner. The authors are not affiliated in any manner with Millennium Laboratories. However, all the authors are members of the American Society of Interventional Pain Physicians (ASIPP) and practicing interventional pain physicians except for Bert Fellows, who is a retired psychologist. Dr. Manchikanti is

the Chairman of the Board and founder of ASIPP, which was responsible for the National All Schedules Prescription Electronic Reporting Act (NASPER) legislation and its implementation. Vidyasagar Pampati, MSc, statistician, is an employee of Ambulatory Surgery Center.

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Role of Sponsor: The financial sponsor of this work had no role in the design and conduct of the study or the collection, management, analysis, and interpretation of the data. The sponsor also did not have a role in the preparation or review of the manuscript or the decision to submit.

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