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Application and Clinical Value of Definitive Drug Monitoring in Pain Management and Addiction Medicine

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Abstract

Objective. To assess routine application and clinical value of definitive urine drug monitoring (UDM) for drug detection, inconsistent drug use, and prescription adherence, along with a comparison to immunoassay screening (IAS). **Methods**. Direct-to-definitive UDM performance was analyzed retrospectively in 5000 patient specimens. Drug findings, medication inconsistencies, and detection sensitivity were assessed, and definitive UDM versus IAS monitoring was studied. **Results**. Definitive testing resulted in 18,793 drug findings with 28,403 positive drug and metabolite tests. Definitive testing expanded monitoring with 11,396 drug findings that would not be tested by IAS. The opioids accounted for the highest frequency of inconsistent positive drug-use findings, at 12%. Conversely, inconsistent negative drug findings, used as an index of prescription non-adherence, were determined in 1,751 of 15,409 monitored medications and included a high frequency of antidepressants and antipsychotics inconsistencies. Direct comparison of definitive UDM and IAS showed false-positives by IAS as well as a high rate of false-negatives that would be missed using current confirmation protocols. **Conclusions**. Results from routine application of direct-to-definitive UDM demonstrate the clinical value of drug-use identification and the objective evaluation of inconsistencies in drug misuse and medication adherence in pain management and addiction medicine practice. Without conversion to direct-to-definitive UDM, continuing use of IAS will limit the scope of drugs being tested, will result in an indeterminate rate of false negatives and will require confirmation testing to eliminate the reporting of false-positive IAS tests. The findings in this study provide evidence-based support for recommended use of a direct-to-definitive drug testing protocol.

Introduction

It is estimated that in the United States 50 million adults live with daily chronic pain [1] and that opioid analgesics have been prescribed for up to one-third of patients with chronic pain treated in primary care clinics [2]. The United States leads the world in the consumption of opioids. According to recent United Nations reports, although the United States represented only 5.3% of the reporting population, it accounted for 99% of hydrocodone, 63% of oxycodone, 45% of hydromorphone, 40% of methadone, 39% of morphine, 20.8% of fentanyl, and 9% of codeine reported use, with a total national consumption of 115 tons of the opioids [3, 4]. Regulatory mandates and standards have been established to guide responsible prescribing of opioids [5–10]. Patients, however, often do not voluntarily report prescription drug misuse or illicit substance-use [11, 12], and some may feign symptoms to obtain opioids for diversion [13], which necessitates objective assessments such as periodic drug monitoring for inconsistent use of both therapeutic and illicit drugs [14]. In the past decade, deaths from fentanyl and related compounds and heroin have also increased [15–28]. An added benefit of drug monitoring includes improved patient adherence to prescribed therapies [29, 30] potentially leading to better patient outcomes and greater trust between provider and patient.

Urine drug monitoring (UDM) has been widely adopted in clinical practice because renal excretion is a major route of drug or metabolite elimination and because detection windows are clinically relevant (i.e., 3 to 5 days) [31, 32]. Presumptive drug testing by IAS has been the dominant practice in drug monitoring because it is rapid, inexpensive and easy to perform. However, false-positive results by IAS can be caused by cross-reactivity with other drugs classes and agents, and less frequently reported is the occurrence of false-negative results due to urine drug concentrations below assay cutoffs [33]. IAS methods cross-reacting within drug classes (e.g., opiates, benzodiazepines, and amphetamine) frequently results in additional interpretive problems that require confirmatory level testing to verify results and identify the specific drug(s) used by the patient [34–37]. In addition, some opioids and benzodiazepines are not well detected by IAS leading to an even higher rate of false negatives within drug classes [34, 38–41].

Definitive UDM, performed increasingly by LC-MS/MS (high performance liquid chromatography- tandem mass spectrometry), provides an alternative to presumptive screening as a direct-to-definitive protocol, and allows selective drug identification with sensitive detection thresholds. Advantages of definitive UDM over IAS include an expanded testing menu, selective determination of parent drug and metabolites, and improved drug-use detection with quantification [34, 42–45]. While definitive testing is currently used primarily to verify unexpected IAS results as a follow-up confirmatory method, recent evidence suggests that definitive testing is more accurate than IAS in assessing patients' substance use as a first line test using a direct-to-definitive protocol [44–47]. Evidence-based consensus studies comparing IAS and definitive UDM have been conducted and now recommend definitive UDM as best practice [48].

In this study we analyze findings and interpretive information resulting from the use of definitive UDM in routine practice and provide an evidence-based evaluation of the recommendation for use of a direct-to-definitive testing protocol. Clinical application and value of definitive UDM is evaluated in a large cohort of samples from pain management and addiction medicine patients. The effectiveness of replacing IAS with a definitive UDM for 95 specific drugs and drug metabolites is evaluated, based on an analysis of drug-use identification and correlation with the patient's medications. Quantitative results by definitive UDM were also analyzed and allowed assessment of the effect of lower cutoffs on drug detection sensitivity. The report also includes direct comparison of definitive UDM and IAS for identification of false-positives, as well as for determination of the false-negatives that result from IAS.

Methods

Patient Sample Cohorts

A definitive cohort of patient specimens monitored by definitive UDM included 5,000 random urine samples obtained, during outpatient encounters between July 2019 and early January 2020, from pain management and addiction medicine patients treated in the Albany Medical Center patient care network. Samples along with a list of current medications were referred for definitive UDM to the National Toxicology Center. The definitive cohort of samples were obtained from 2,236 male patients with ages ranging from 18 to 80 years (mean 44 years) and 2,764 female patients aged 18 to 87 years (mean 45 years). The cohort study did not include access to the medical record and the exported data did not include patient identifiers. Since some patients may have been monitored periodically during the 6-month study period, repeat monitoring results were included in the study. An additional IAS cohort of 217 urine samples was initially screened by IAS methods at an Albany Medical Center Network Hospital and referred to the National Toxicology Center for further testing due to presumptive positive screening results. The IAS cohort of samples was obtained from 101 male patients with ages ranging from 25 to 69 years (mean 42 years) and 116 female patients aged 26 to 73 years (mean 47 years). The IAS follow-up testing included the full panel of definitive UDM tests resulting in confirmation testing for both negative and positive IAS test results, as well as expanded screening for drugs not tested initially by IAS. The study protocol, analyzing de-identified test results along with demographics,

medication listings, and interpretive report comments, was reviewed and authorized by the Institutional Review Board of the Albany Medical College.

Definitive and IAS Methods

Definitive UDM was performed at the National Toxicology Center by a previously reported UPLC-MS/MS calibration technique and method for quantitative determination of 64 drug and metabolites including opiates, opioids, opioid antagonists, benzodiazepines, amphetamines, gabapentinoids, illicits, and other drugs that are ordered in pain management and addiction medicine practice [45, 49]. The method was expanded to include antidepressants and antipsychotics to monitor adherence with psychiatric medications, and the method was further validated for concordance with stable isotope dilution and high-resolution mass spectrometry methods of drug testing [50, 51]. The selection of drug panel tests was based on experience in both clinical and forensic toxicology and on interaction with clinical providers in pain management and addiction medicine. Drugs and metabolites in the definitive panel, along with their limit of detection (LOD), lower limit of quantitation (LLQ) and upper limit of quantitation (ULQ), are listed in Table 1. The clinical testing protocol includes evaluation of test results in relation to the submitted medication list information, with toxicologist oversight, and the method was authorized for patient testing by New York State Department of Health and CLIA. Briefly, the definitive method involves automated sample preparation using a Microlab STARlet liquid handling system (Hamilton Company, Reno, NV, USA) with enzymatic hydrolysis of glucuronide-conjugated drugs and drug metabolites. Samples for batch testing of up to 130 patient samples were analyzed by UPLC-MS/MS (ACQUITY I-Class-Xevo TQD, Waters Corp. Milford MA), using a rapid 3.3-minute mass spectrometry acquisition program with next-day turnaround of results with interpretation.

IAS methods of drug screening were performed on a Roche Cobas c501 (Roche Diagnostics Corporation, Indianapolis, IN, USA) using 11 FDA approved IAS methods. Positive IAS cutoff concentrations for amphetamines (500 ng/mL), benzodiazepines (200 ng/mL), buprenorphine (10 ng/mL), cocaine metabolite (150 ng/mL), fentanyl (1 ng/mL), hydrocodone (100 ng/mL), methadone (300 ng/mL), opiates (300 ng/mL), 6-acetylmorphine (10 ng/mL), oxycodone (100 ng/mL), and phencyclidine (25 ng/mL) were used as specified by assay manufacturers. The fentanyl IAS was supplied by Ark Diagnostics Incorporated (Fremont, CA, USA). Hydrocodone and 6-acetylmorphine assays were from Lin-Zhi International, Inc (Santa Clara, CA, USA) and all other assays were supplied by Roche Diagnostics Corporation (Indianapolis, IN, USA). IAS results were reported qualitatively as positive when at or above the cutoff concentration and as negative when below the cutoff level. Interpretive reporting of IAS results was not performed.

Study Design and Data Analysis

Definitive drug test results along with demographics and inconsistency data were exported from the National Toxicology Center's Toxicology Information Management System database with removal of all patient identifiers. Statistical analysis of the data was performed using Microsoft Excel software (Redmond WA) without statistical correction for repeat patient testing. Inconsistent positive drug-use findings included illicit drug findings, therapeutic drugs not listed in the medication information, or test result patterns indicative of medication simulation. Inconsistent negative drug-use findings included tests with negative results for therapeutic drugs included on the medication list. Inconsistency was not determined for nicotine use because social history regarding use of tobacco products or nicotine vaping was not included with the medication information.

In accordance with the study design, definitive cohort data was initially analyzed to determine the number of positive drug and metabolite test findings. The quantitative results for positive drug and metabolite testing were analyzed and used to predict the decrease in detection sensitivity associated with the higher cutoff thresholds used in IAS. Clinically relevant data on drug use, interpreted from drug and metabolite test results, were also analyzed to determine the frequency of illicit and therapeutic drug use in the definitive cohort. The drug-use findings were correlated with the prescription data to identify the number and frequency of inconsistent positive and negative drug-use findings in the cohort. Additional analysis was performed on data from the IAS cohort which included parallel testing by IAS and definitive UDM. The IAS cohort provided an opportunity to evaluate the false negative rate of IAS and to determine any additional drug findings resulting for the expanded scope of definitive UDM. Analysis also included assessment of false-positives by IAS.

Results

Frequency of Positive Tests and Drug-Use Findings by Definitive UDM

Definitive UDM resulted in 28,403 positive tests for parent drugs and their metabolites in the definitive cohort as shown in Figure 1. Nicotine's metabolite, cotinine, was the most frequent positive test finding with a 73% positivity rate. Next most frequent positive tests were buprenorphine and its metabolite, norbuprenorphine, with positivity rates of 50% and with concomitant naloxone therapy detected in 76% of the buprenorphine positive cases. A total of 79 specific drugs and metabolites were detected in the cohort at the frequencies shown in Figure 1. Definitive UDM significantly expanded the number of drugs tested compared with IAS as displayed

Table 1. Drugs and metabolites tested in the definitive UDM are listed by drug class with analytical limit of detection, lower limit of quantitation, and upper limit of quantitation

	Detection Limit	Lower Limit of Quantitation	Upper Limit of Quantitation
DRUG CLASS:			
Drug/metabolite tested	ng/mL	ng/mL	ng/mL
AMPHETAMINES:			
Amphetamine	20	50	1,000
Methamphetamine	20	50	1,000
Phentermine	20	50	1,000
Pseudoephedrine	20	50	1,000
BENZODIAZEPINES:			
Alprazolam	20	50	1,000
Alprazolam, α-OH	20	50	1,000
Clonazepam	20	50	1,000
Clonazepam, 7-amino	20	50	1,000
Diazepam	20	50	1,000
Diazepam, nor	20	50	1,000
Flurazepam	20	50	1,000
Flurazepam, OH ethyl	20	50	1,000
Lorazepam	20	50	1,000
Midazolam	20	50	1,000
Oxazepam	20	50	1,000
Temazepam	20	50	1,000
Triazolam	20	50	1,000
Triazolam, α-OH	20	50	1,000
ANTIDEPRESSANTS:			
Amitriptyline	20	50	1,000
Bupropion	20	50	1,000
Amoxapine	20	50	1,000
Citalopram	20	50	1,000
Clomipramine	20	50	1,000
Desipramine	20	50	1,000
Duloxetine	20	50	1,000
Doxepin	20	50	1,000
Doxepin, nor	20	50	1,000
Duloxetine	20	50	1,000
Fluoxetine	20	50	1,000
Fluoxetine, nor	20	50	1,000
Fluvoxamine	20	50	1,000
Imipramine	20	50	1,000
Mirtazapine	20	50	1,000
Nortriptyline	20	50	1,000
Sertraline	20	50	1,000
Sertraline, nor	20	50	1,000
Trazadone	20	50	1,000
ANTIPSYCHOTICS:			
Chlorpromazine	20	50	1,000
Clozapine	20	50	1,000
Fluphenazine	20	50	1,000
Haloperidol	20	50	1,000
Iloperidol	20	50	1,000
Lurasidone	20	50	1,000
Olanzapine	20	50	1,000
Quetiapine	20	50	1,000
Risperidone	20	50	1,000
Thioridazine	20	50	1,000
Ziprazidone	20	50	1,000
ECSTASY:			
MDA	20	50	1,000
MDEA	20	50	1,000
MDMA	20	50	1,000
DRUG CLASS:			
Drug/metabolite tested	ng/mL	ng/mL	ng/mL
DEXTROMETHORPHAN:			
Dextromethorphan	20	50	1,000
Dextrorphan	20	50	1,000
GABAPENTINOIDS:			
Gabapentin	200	500	10,000
Pregabalin	100	250	5,000
ILLICITS:			
Cocaine (Benzoylecgonine)	10	25	500
Heroin (6-acetyl morphine)	2	5	100
Phencyclidine	2	5	100
KETAMINE:			
Ketamine	2	5	100
Ketamine, nor	2	5	100
METHYLPHENIDATE:			
Methylphenidate	20	50	1,000
Ritalinic acid	20	50	1,000
MUSCLE RELAXANTS:			
Carisoprodol	20	50	1,000
Cyclobenzaprine	20	50	1,000
Meprobamate	20	50	1,000
MITRAGYNINE:			
Mitragynine	2	5	100
Mitragynine, 7OH	2	5	100
OPIOID ANTAGONISTS:			
Naloxone	20	50	1,000
Naltrexone	20	50	1,000
OPIOID ANALGESICS:			
Codeine	20	50	1,000
Dihydrocodiene	20	50	1,000
Hydrocodone	20	50	1,000
Hydromorphone	20	50	1,000
Morphine	20	50	1,000
Oxycodone	20	50	1,000
Oxycodone, nor	20	50	1,000
Oxymorphone	20	50	1,000
Oxymorphone, nor	20	50	1,000
Buprenorphine	2	5	100
Buprenorphine, nor	2	5	100
Fentanyl	1	2	50
Fentanyl, nor	1	2	50
Meperidine	20	50	1,000
Meperidine, nor	20	50	1,000
Methadone	20	50	1,000
EDDP	20	50	1,000
Tramadol	20	50	1,000
Tramadol, n-desmethyl	20	50	1,000
Tapentadol	20	50	1,000
SEDATIVES:			
Zaleplon	20	50	1,000
Zolpidem	20	50	1,000
SYNTHETIC STIMULANTS:			
Ethylone	2	5	100
MDPV	2	5	100
Alpha-PVP	2	5	100
OTHER DRUGS:			
Cotinine	20	50	1,000

Noroxymorphone (N-desmethyl oxymorphone), nornaloxone (N-despropene naloxone) and nornaltrexone (N-descyclopropylmethyl naltrexone) are structurally identical and co-analyzed in the noroxymorphone test.

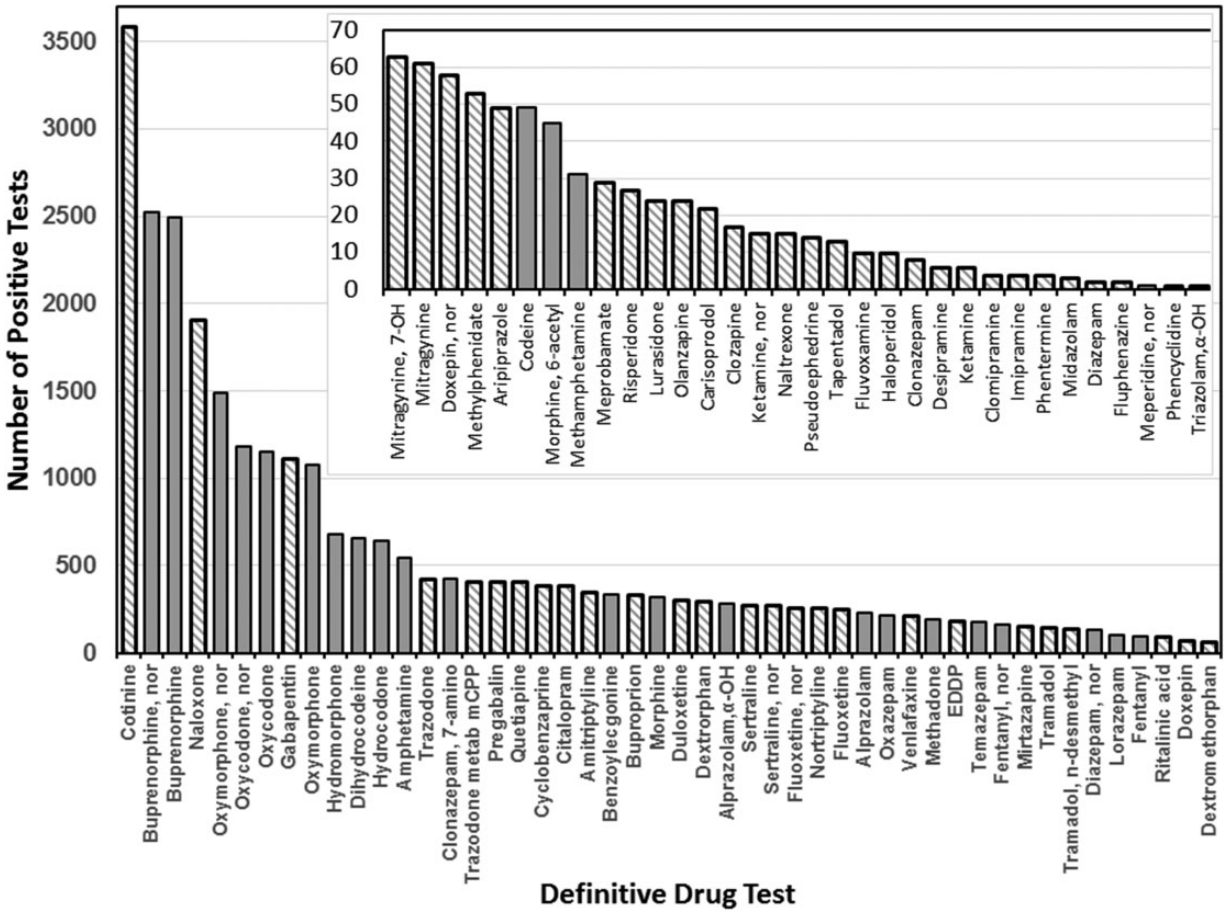

Figure 1. Frequency of positive tests by definitive UDM in 5,000 urine specimens. The inserted graph further displays lower frequency positive tests. The hatched bars in both graphs show the drugs and drug metabolites not tested by the eleven immunoassay methods employed in the immunoassay cohort study.

in hatched bars. The expanded testing by definitive UDM resulted in an additional 13,238 positive drugs and metabolites that were not tested by IAS.

Definitive UDM allows a drug and metabolite evaluation of drug-use by the patient. For example, oxycodone use is determined by testing for oxycodone along with three of its metabolites (noroxycodone, oxymorphone, and noroxymorphone) and both the identification as well as the pattern of quantitative results for these tests underlies a reported finding of oxycodone use. The laboratory report also includes the quantitative drug and metabolites findings along with an interpretive comment on drug-use identification. In the definitive cohort 18,793 drug-use findings were reported and the highest frequency of drug-use by drug class was opiates/opioids (5,225) followed by antidepressants (3,038), gabapentinoids (1,524), benzodiazepines (1,021), amphetamines (590), antipsychotics (516), and muscle relaxants (418).

Prescribed Medication Monitoring by Definitive UDM

A list of current medications was submitted with each order for definitive drug testing and it should be noted that the accuracy of the list was based on the medication review and reconciliation process at each practice site. The frequency of medications tested for in the definitive cohort is shown in Table 2. A total of 15,409 medications were monitored in the definitive cohort samples and approximately 50% of the samples were from patients prescribed buprenorphine for addiction therapy, with 89% of these patients treated with a buprenorphine formulation containing naloxone. The frequency of prescriptions for psychiatric medications was also high in this cohort. In order of frequency, prescriptions for buprenorphine and other opiate/opioids were highest (5,045 prescriptions), followed by antidepressants (3,728), opioid antagonists (2,254), gabapentinoids (1,600), benzodiazepines (895), antipsychotics (862), muscle relaxants (513), and amphetamines (329).

Inconsistent Positive Drug-Use Findings by Definitive UDM

Inconsistent positive findings were reported for use of an illicit drug or use a of therapeutic drug not listed as a current medication. Testing that showed a simulated drug pattern such as high parent drug concentration without

Table 2. Monitored medications listed in the definitive cohort cases

Drug	Number Prescribed	Drug	Number Prescribed	Drug	Number Prescribed
Buprenorphine	2,497	Zolpidem	249	Fentanyl	35
Naloxone	2,218	Fluoxetine	247	Carisoprodol	25
Oxycodone	1,251	Alprazolam	235	Lurasidone	25
Gabapentin	1,181	Venlafaxine	235	Olanzapine	21
Hydrocodone	715	Morphine	206	Codeine	10
Quetiapine	573	Methadone	183	Tapentadol	10
Trazodone	555	Mirtazapine	180	Clozapine	9
Duloxetine	534	Tramadol	138	Dextromethorphan	9
Cyclobenzaprine	488	Lorazepam	100	Haloperidol	9
Buproprion	471	Diazepam	98	Fluvoxamine	6
Clonazepam	460	Risperidone	75	Fluphenazine	4
Pregabalin	419	Doxepin	61	Zaleplon	3
Cotinine	396	Diazepam	98	Imipramine	2
Amitriptyline	376	Risperidone	75	Phentermine	2
Citalopram	375	Doxepin	61	Triazolam	2
Amphetamine	327	Methylphenidate	55	Chlorpromazine	1
Sertraline	301	Naltrexone	36	Ziprazidone	1

significant metabolite findings were also reported as inconsistent. Analysis of the cohort revealed 2,241 inconsistent positive drug findings including illicits, prescribed therapeutics, and over-the-counter drugs at frequencies displayed in Figure 2. Illicit use of cocaine was the most frequent inconsistency, followed by use of the over-the-counter agent, dextromethorphan, and nonprescribed use of gabapentin. The frequency of inconsistent positives by drug class was highest for the opiates/opioids (487) followed by illicit drugs (469), benzodiazepines (341), gabapentinoids (218), amphetamines (156), antipsychotics (55), antidepressants (50), and muscle relaxants (12). The frequency of inconsistent positive drug findings compared to total positive findings for the drug allowed an assessment of the rate of inconsistent drug misuse for therapeutic agents. Drugs with percent misuse rates greater than 50% included codeine (77.4%), fentanyl (69.1%), diazepam (63.8%), methylphenidate (60.0%), and alprazolam (52.9%). Positive findings for these drugs have a greater than 50% probability of indicating misuse based upon inconsistent findings in the cohort. Gabapentin had the second highest number of inconsistent positive findings but the rate of misuse (15.1%) was not among the highest in the study due to the frequency of prescribed gabapentin use. Inconsistency or misuse rates were among the lowest for buprenorphine (2.9%) and naloxone (3.5%) therapy.

Inconsistent Negative Drug Findings by Definitive UDM

Negative drug use findings with prescribed medications allowed objective evidence of either non-adherence with current prescribed therapy or inaccuracy in the medication reconciliation process. In samples with inconsistent negative findings the concentrations of the monitored drugs and their metabolites were less than the analytical LODs as listed in Table 1. Figure 3 shows the frequency of inconsistency for negative drug findings in the definitive cohort. A total of 1,751 prescribed drugs were not associated with test evidence of drug use, representing an overall 11.4% inconsistency rate for prescription drugs. Antidepressant (630) and antipsychotic (256) medications were prominent among the inconsistent findings with 19% of antidepressant and 28% of antipsychotics prescriptions lacking definitive UDM evidence of medication-associated positive drug findings.

Detection Sensitivity in Definitive UDM

Drugs and metabolites in the definitive cohort were stratified by concentration to evaluate the change in drug detection sensitivity with a progressive lowering of the positive cutoff concentration. Figure 4 displays the change in drug detection for representative drugs and their metabolites. Threshold cutoffs were evaluated at IAS cut-off concentration down to those applied with definitive UDM testing. Lowering the cutoffs increased the detection rate for all drug and metabolite tests as displayed in the figure, except for parent drug monitoring of diazepam and clonazepam which both lacked detection sensitivity even at the low definitive UDM detection limit. Although absolute detection sensitivities differed for each drug and its metabolite(s), a parallel trend toward greater detection sensitivity at lower thresholds was observed. The analysis also shows that combined drug and metabolite(s) monitoring adds certainty to a positive drug determination by definitive UDM. Similar patterns of increasing detection rate at lower cutoffs were observed for other tests in the definitive UDM panel. The study also reveals the relative sensitivity of detection of parent drug and its metabolite testing. The drug or drug metabolite with optimum sensitivity is shown in parenthesis for use of clonazepam (7-aminoclonazepam),

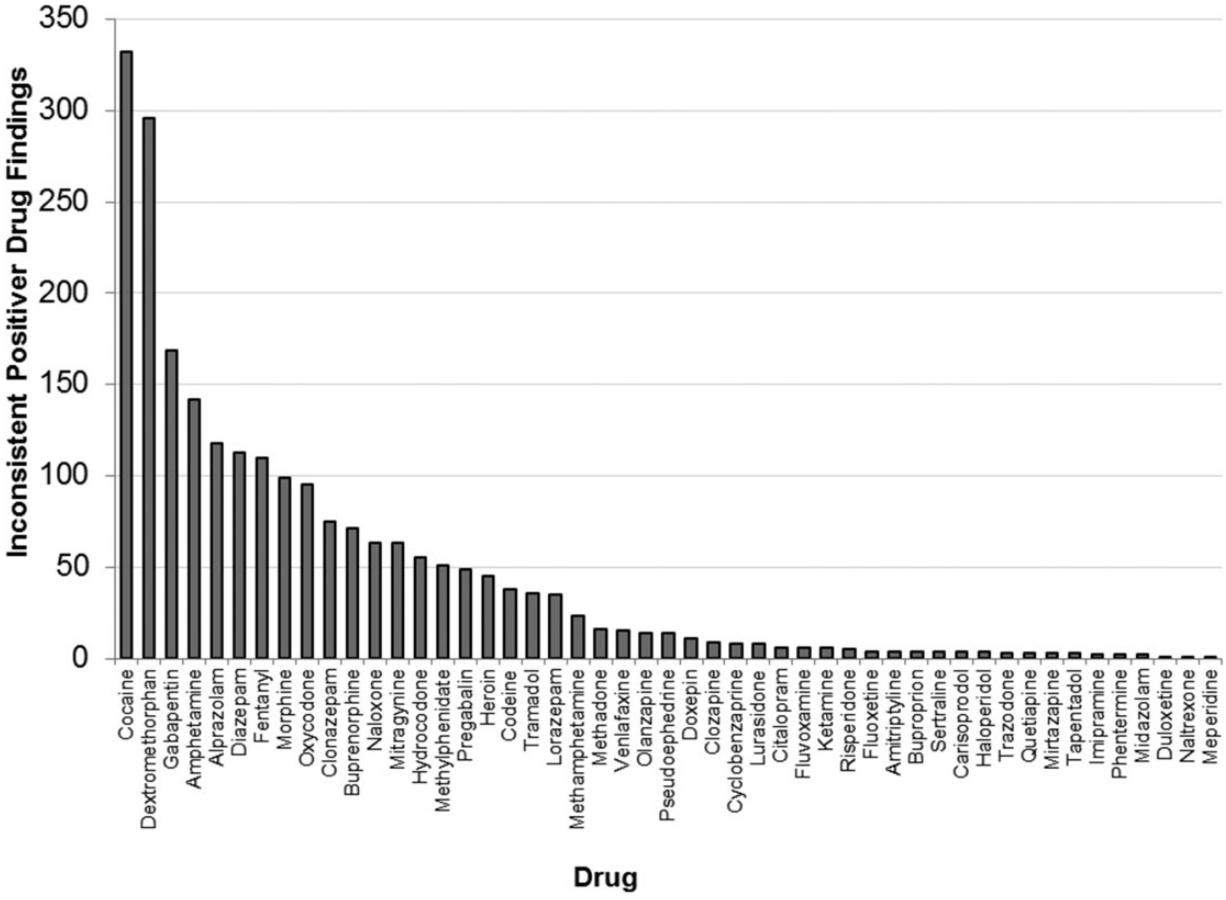

Figure 2. Frequency plot for 2,241 inconsistent positive drug findings evaluated in relation to medication information provided in the case.

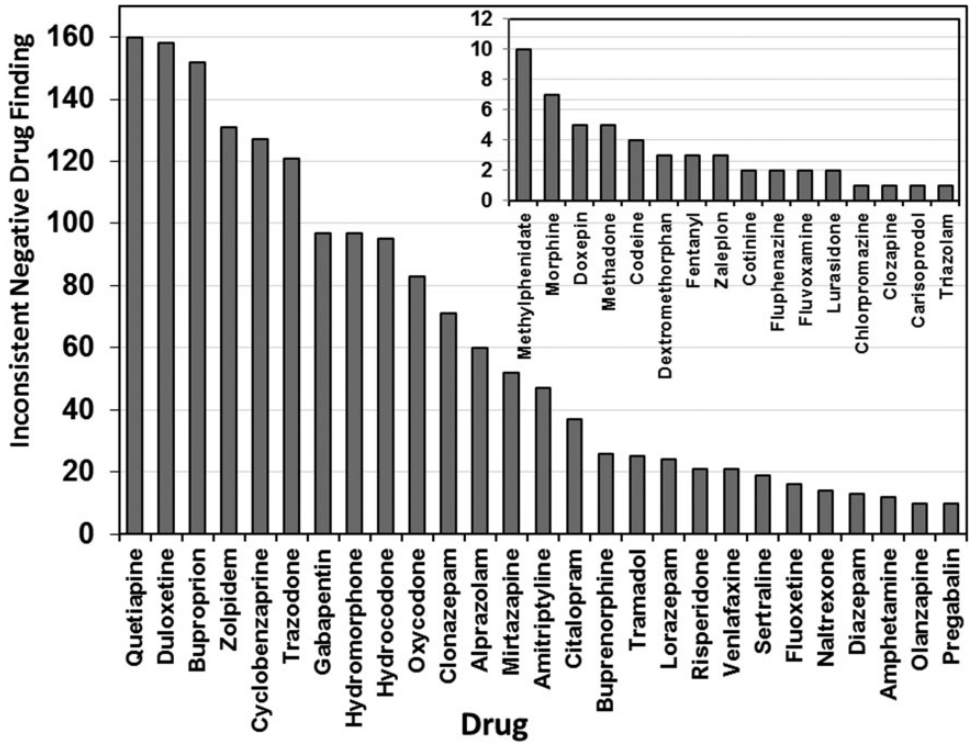

Figure 3. Frequency plots of the drug therapy listings with inconsistent negative testing by definitive UDM. The inserted plot displays the lower-frequency prescribed therapeutics with inconsistent findings.

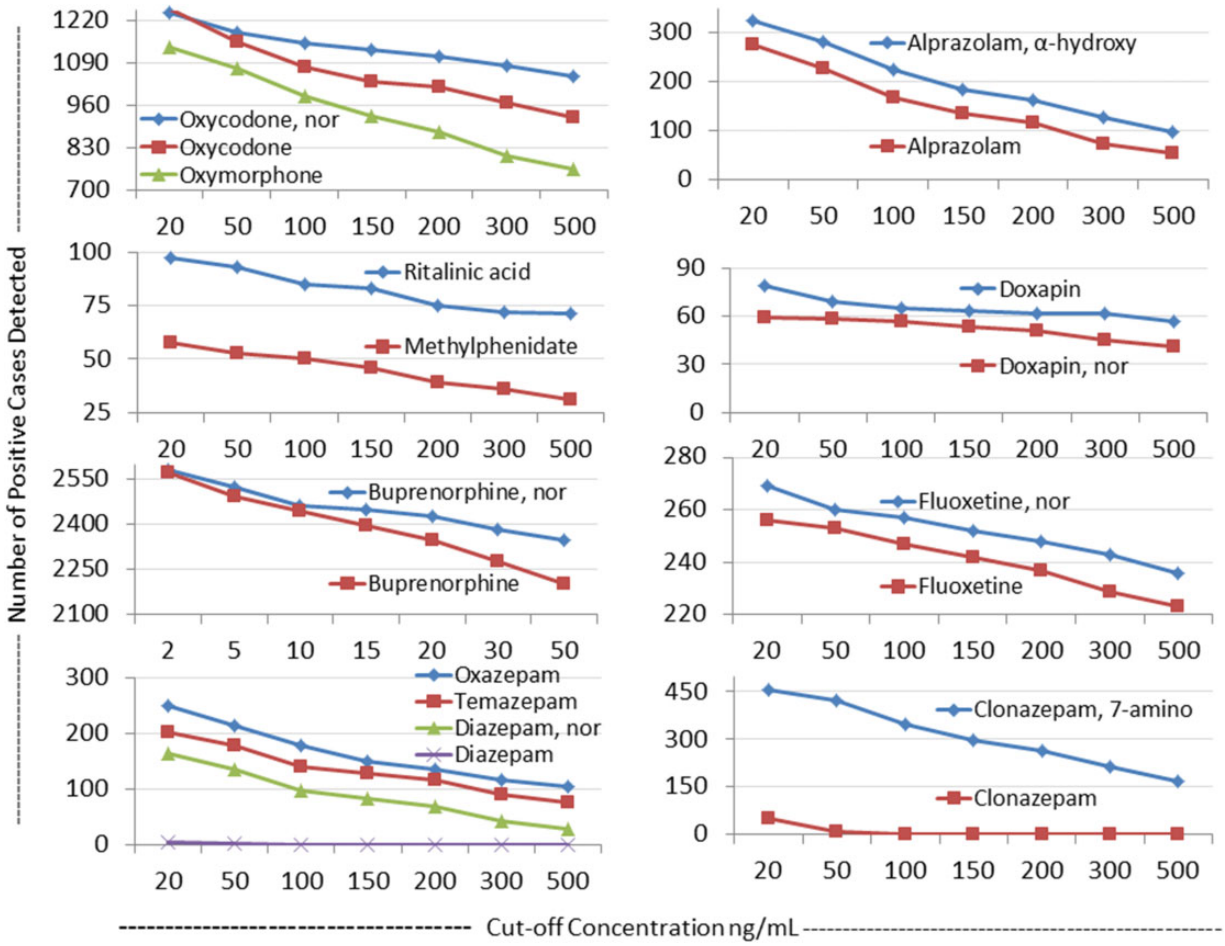

Figure 4. Detection sensitivity plots for representative drugs and their metabolites showing the relationship between progressive decrease in threshold concentration and the increase in detection rate in the definitive cohort of specimens.

diazepam (oxazepam), alprazolam (α-hydroxyalprazolam), oxycodone (noroxycodone), doxepin (doxepin), methyphenidate (ritalinic acid), fluoxetine (norfluoxetine), buprenorphine (norbuprenorphine), fentanyl (norfentanyl), and mitragynine (7-hydroxymitragynine).

The concentration stratification was also used to predict the rate of false negative findings with use of the higher cutoffs applied in IAS. Definitive UDM for cocaine showed that 109 benzoylecgonine-positive samples had cocaine metabolite concentrations below the cocaine IAS threshold of 150 ng/mL, predictive of a 33% false-negative rate for detecting use of cocaine by IAS. In a similar analysis of morphine detection, a false-negative rate of 16% was predicted with 51 morphine positive cases containing morphine concentrations below the 300 ng/mL cutoff of the opiate IAS. An even higher rate of false-negatives was predicted for alprazolam (42%) and clonazepam (37%) in the benzodiazepine IAS.

IAS and Definitive UDM Performance Comparison

A direct comparison of IAS and definitive UDM testing was studied in the IAS cohort of 217 urine specimens, which were initially screened by IAS and then tested by the definitive UDM method. As shown in Table 3, definitive UDM identified 507 positive drugs within the drug classes monitored by IAS. Definitive UDM findings included 60 positive drugs that were not detected by IAS, resulting in false-negative rates by IAS as shown in Table 3. The highest false-negative rates were found for the benzodiazepine, cocaine and opiates IAS methods and these rates were comparable to the false-negative rates predicted from the cutoff-stratification study reported above for the definitive cohort. The method comparison study also revealed an additional 217 positive drug findings by definitive UDM resulting from the expanded panel of drug and metabolite testing performed by the definitive method. The method comparison also showed a false-positive rate by IAS as displayed in Table 2 with the highest false-positive rates for phencyclidine, hydrocodone, and amphetamines by IAS.

Discussion

Definitive methods of drug monitoring in the clinical toxicology laboratory have greatly expanded the number of clinically relevant drugs and metabolites that can be tested and reported in support of pain management and

Table 3. Comparison of immunoassay performance based upon and definitive UDM results in 217 urine specimens from outpatients treated in an addiction medicine practice

	Definitive UDM Results					Immunoassay Performance				Number of Additional Definitive UDM Findings	
	Definitive Negatives	Definitive Positives	Drug Prevalance	True Negatives	True Positives	False Negatives		False Positives			
Drug Class	(DN)	(DP)	DP/217 (%)	(TN)	(TP)	(FN)	FN/DP (%)	(FP)	FP/(FP+DP) (%)	Naloxone	110
Amphetamine	149	68	31%	92	66	2	3%	57	46%	Gabapentin	49
Benzodiazepines	164	53	24%	163	29	24	45%	1	2%	Pregabalin	12
Buprenorphine	74	143	66%	74	139	4	3%	0	0%	Pseudoephedrine	10
Cocaine	172	45	21%	172	30	15	33%	0	0%	Dextromethorphan	9
Fentanyl	155	62	29%	148	62	0	0%	7	10%	Tramadol	7
Heroin	211	6	3%	211	6	0	0%	0	0%	Methylphenidate	5
Hydrocodone	193	24	11%	170	24	0	0%	23	49%	Mitragynine	5
Methadone	204	13	6%	200	12	1	8%	4	24%	Zolpidem	4
Opiates	175	42	19%	174	29	13	31%	1	2%	Carisoprodol	2
Oxycodone	166	51	24%	166	50	1	2%	0	0%	Ketamine	1
PCP	217	0	0%	214	0	0	0%	3	100%	Phentermine	1
										Naltrexone	1

addiction medicine practice. Expansion in the scope of testing has occurred in response to over a decade of proliferation and enhanced use of therapeutic, illicit, and other drugs that are not being tested in traditional drug screening protocols. Application of definitive UDM is a paradigm shift away from the standard drug screening protocol which has relied on presumptive IAS of drug classes followed by definitive confirmation testing for only screen-positive IAS results. The current study of routine laboratory experience shows that conversion to direct-to-definitive UDM is achievable with LC-MS/MS technology. The laboratory transition, from use of definitive technology for only confirmation testing to use in high volume screening, required development and validation of large multi-drug testing methods. Direct-to-definitive UDM testing was achieved with automated sample preparation, rapid chromatography and mass spectrometry acquisitions, and an informatics management system for handling the large volume of test and quality control data. As reported by Chau and coworkers, provider misinterpretation can be a significant problem when only the test results of definitive UDM are reported to the clinician [52]. Definitive UDM in the current study employed toxicologist-guided evaluation of drug-use findings with issuance of an interpretive laboratory report that minimized the need for in depth clinician knowledge of metabolic pathways or other nuances of laboratory drug testing. Turnaround time is also an important element in the clinical application of definitive UDM and next day turnaround for batch testing was found to be at least comparable or better than the experienced turnaround time for presumptive screening followed by definitive retesting for positive IAS results.

Outcomes of Direct-to-Definitive UDM

Application of direct-to-definitive UDM in the definitive cohort has been evaluated for clinical value in selective identification of drug use by the patient. Definitive monitoring resulted in over 28,000 positive drug and metabolite test results. Opiates and opioids dominated the positive test findings and the testing for gabapentinoids, benzodiazepines, amphetamines, antidepressants, antipsychotics, mitragynine, muscle relaxants, and illicit drugs added to a more complete understanding of current drug use by the patients.

Monitoring of drugs along with their metabolites adds to drug-use detection and certainty, as well as to the evaluation of formulation differences and sample adulteration in some cases. In detection of diazepam use for example, diazepam testing is very insensitive, but coanalysis of the metabolites oxazepam, temazepam, and nordiazepam add sensitivity and certainty to the finding of diazepam use. In buprenorphine usage, coidentification and quantification of buprenorphine and norbuprenorphine was found to be effective in both identifying drug use and also in distinguishing buprenorphine

use from a medication simulation by sample tampering. Naloxone monitoring also distinguishes between uses of buprenorphine formulations, allowing inconsistency evaluations based upon formulation-level identifications. Metabolites of oxycodone showed value in assessing oxycodone use with codetection and quantification of oxycodone and its metabolites noroxycodone, oxymorphone and noroxymorphone. A different pattern of oxycodone and its metabolites is routinely observed in naloxone and naltrexone therapy. Noroxymorphone (N-desmethyl oxymorphone) is a metabolite of oxycodone but is also structurally identical to metabolites of nornaloxone (N-despropene naloxone) and nornaltrexone (N-descyclopropylmethyl naltrexone) and findings of these metabolites in naloxone or naltrexone therapy without the detection of oxycodone, noroxycodone and oxymorphone is another interpretive advantage of definitive UDM. These and other examples of metabolites interpretation demonstrate the clinical value to interpretive laboratory reporting for definitive UDM.

Specific identification of drug-use by definitive UDM also allowed a correlation with current medication information and an assessment of inconsistent drug findings that include illicits and therapeutics. Opiates and opioids were the most frequent drug class misused followed in order by benzodiazepines, gabapentinoids, and amphetamines. Benzodiazepine misuse was prominent in the cohort with an order of frequency of alprazolam > diazepam > clonazepam > lorazepam. The total number of gabapentin inconsistencies was 169, and gabapentinoid misuse has been reported by others [53–57]. Although the overall rate of gabapentin misuse was not among the highest because of the high prevalence of gabapentin therapy, the actual number of inconsistent gabapentin-use findings was high and consistent with reports of gabapentin misuse. The very low inconsistency rate for buprenorphine and naloxone suggested that combination buprenorphine-naloxone therapy for addiction treatment has a relatively lower rate of misuse by the patients in the definitive cohort. Inconsistent use of cocaine and other illicit drugs was found with a frequency order of cocaine > heroin > methamphetamine > ketamine. An association between fentanyl, heroin and morphine was observed in the study, consistent with the findings of fentanyl in heroin seizures by law enforcement. Illicit methamphetamine use was identified in 26 cases, and the distinction of therapeutic amphetamine use versus illicit methamphetamine use is another advantage of front-line application of definitive UDM.

Other agents and designer drugs have been considered for inclusion in the definitive UDM panel based on reported use in our region of testing. The plant alkaloid mitragynine, for example, has been included in the testing panel as a result of reported use for both its opioid-like effect and its use in reducing withdrawal effects from opioid abuse [58–60]. All cases of mitragynine use are reported as inconsistent both because it not being listed as a medication and because of the regional differences in the legal status of mitragynine. The synthetic stimulants and cathinones (ethylone, MDPV, and alpha-PVP) in the definitive UDM panel were not detected in the definitive cohort indicating a cessation in regional use of these designer drugs. The over-the-counter drug, dextromethorphan, was ranked second in inconsistent frequency. While medication reconciliation may be a factor in this high rate of inconsistency, dextromethorphan misuse among opioid-dependent patients has been recently studied and analysis of dextromethorphan in hair was identified in 11.5% of the patients [61]. Cotinine inclusion in the definitive UDM panel of testing provides the clinician with an objective measure of nicotine use by the patient and may be useful in counseling. Social history was not provided along with the medication information so it was not possible to determine consistency with nicotine use except in cases where cessation therapies with nicotine pack was indicated on the medication list.

Adherence with prescribed therapeutic medication may also affect patient outcomes and the need for measures of adherence has been reported [62]. The study shows definitive UDM may provide the clinician with objective evidence of adherence or non-adherence with prescribed drug and testing for prescription adherence as an integral part of the definitive UDM testing protocol. Buprenorphine and naloxone monitoring in the definitive cohort showed adherence with therapy in over 99% of monitored samples. Lower rates of adherence were found for other prescribed drugs, most notably the antidepressants and antipsychotics. Prescribed psychiatric medications with negative drug findings occurred with bupropion (32%), duloxetine (30%), mirtazapine (29%), quetiapine (28%), risperidone (28%), trazadone (22%), amitriptyline (13%), clozapine (11%), citalopram (10%), venlafaxine (9%), sertraline (7%), and fluoxetine (7%). The challenge of patient adherence with antidepressant and antipsychotic medications is known and UDM has been recommended for serious mental illness [63–68]. It should also be noted that use of psychiatric medications without a prescription was also found, as shown in Figure 2. The relatively high frequency of psychiatric therapeutic usage in pain management and addiction medicine patients coupled with the inconsistency findings in this study support the need for expanded monitoring of psychiatric medications.

Study Limitations

The frequency of inconsistent findings in this laboratory-based study of definitive UDM has limitations in predicting the incidence of inconsistencies in a pain management or addiction medicine practice. All test results were de-identified, and it was not possible to link tests to a specific individual, and the cohort includes both initial and follow-up specimens. The inability to link specimen results to a specific patient also limited development of

multi-regression models to investigate the associations between various positive test results. Also, the cohort was comprised of individuals receiving treatment for substance use disorders and chronic pain, and the data collection protocol does not allow distinction between these patient populations. In routine use of definitive UDM, inconsistent positive and negative drug finding are communicated directly to the practitioner through the laboratory report, allowing a practice-based follow-up with the patient and an improved knowledge by the practitioners of the frequency of drug misuse and nonadherence within their practice. Another limitation of a laboratory-based study is the inability to correct for any inaccuracies in the medication information submitted in the testing process. Again, in routine practice medication reconciliation can be conducted when an inconsistency is reported by the laboratory and inaccuracies in medication documentation can be corrected at the practice level.

Implications of False IAS Results

Definitive UDM was also compared with the widely used practice of IAS. While false-positive IAS results are frequently identified in routine confirmation testing and reported in the literature [35–37, 69], knowledge of the rate of false negative testing by IAS is more limited. The IAS cohort data included definitive confirmation for both positive and negative IAS findings as well as expanded testing for drug use not tested by immunoassay. False negatives were identified in IAS for amphetamine, benzodiazepine, buprenorphine, cocaine, methadone, opiate and oxycodone testing by IAS with the highest rates of false negatives for benzodiazepines, cocaine and opiates. Cocaine IAS, for example, missed 15 cases of cocaine use for a 33% false negative rate. The relatively high cutoff concentrations used in IAS testing appear to be the main cause of these false-negative findings. Actual (IAS cohort) and predicted (definitive cohort) false-negative rates for cocaine testing were the same (33%). The actual false negative benzodiazepine rate was 45% with the predicted rate based on concentration stratification studies ranging up to 45% depending upon the specific benzodiazepine tested. The combined findings in the definitive and IAS cohorts showed that the lower thresholds used in definitive UDM are more sensitive in the detection of drug use. Consistent with our findings, others have reported false-negative results by IAS, and others have reported that the lower cutoffs by definitive testing correlate with better patient adherence assessment [62, 70].

False-positive IAS results were also identified in the IAS cohort. In principle, IAS cross-reactivity with drugs within a particular drug class (e.g., benzodiazepines, opiates, and amphetamines) provides a multi-drug approach to drug screening with a limited number of tests. Cross-reactivity with agents and drugs outside the drug class however caused false-positive screen results [35–37] and our study shows that the rate of false-positive for IAS was as high as 100% (phencyclidine) with next highest false-positive rates for amphetamine and hydrocodone. The frequency of false-positives reaffirm the need for confirmatory testing for IAS.

Considerations for Widespread Adoption

The current study demonstrates the clinical benefits of direct-to-definitive UDM as an alternative to the traditional IAS test protocol. Ultimately, the widespread application of direct-to-definitive UDM in routine practice will be determined by clinical test value and by availability of cost effective direct-to-definitive testing. Current advances in automation and data management have made inroads into the application of definitive UDM in high-volume drug testing. Recent reports have also begun to address the economics of conversion to direct-to-definitive testing and have built a combined economic, regulatory and best practice case for the definitive testing based on decreasing cost of mass spectrometry, evolving opioid regulations, changing reimbursement practices and clinical value of definitive test findings [47, 71]. Definitive testing likely will provide overarching cost and health benefits for numerous reasons. Such considerations include patient safety by referral for appropriate behavioral health intervention, resultant potential reduction in emergency rooms for inadequate pain control, reduced incidence of drug-drug interactions or drug-seeking and decreased risk of overdose. Moreover, there is potential for considerable cost reduction to third party payers for drugs that are prescribed but are not actually being used by those for whom they are intended—consider for example the cost of a year's worth of extended release oxycodone if only a fraction of the prescribed drug is utilized by the patient, and the rest is diverted.

Conclusion

Retrospective analysis of drug-use findings with objective evaluation of both medication misuse and adherence demonstrate the applicability and clinical benefits of direct-to-definitive UDM in pain management and addiction medicine practice. Use of presumptive screening by IAS limits the scope of drug testing and results in both false-negative and false-positive screening tests. The study provides evidence-based support for recommended adoption of direct -to-definitive UDM as best practice.

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