

Quantitative Urine Drug Monitoring in Methadone Programs: Potential Clinical Uses

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Abstract—An on-site clinical laboratory in a methadone program can provide semiquantitative urine drug monitoring by using fluorescence polarization immunoassay (FPIA) technology. This report documents a wide range of urine drug levels from threshold to near 2,000,000 ng/ml in this patient population, suggesting how laboratory measures can assist in assessing the severity of addiction. Urine drug-level data are reported for drugs of abuse (opioid, amphetamines, cocaine) as well as therapeutic drugs (benzodiazepines and methadone). Clinical uses of quantitation illustrated include screening of all admissions prior to induction on methadone, identification of unusually heavy users, monitoring drug washout, and assessing compliance with prescribed benzodiazepine and methadone regimens. The Clinical Laboratory Improvement Act (CLIA 88) has set national certification standards for moderate complexity laboratories using immunoassays and set up a mechanism for monitoring quality in such clinic-based laboratories.

Keywords—drugs, methadone, on-site laboratory, quantitative, urine testing

Historically, urine drug tests have been reported as qualitative, positive or negative results. Quantification of urine test results has not received much scientific attention because it has been assumed that qualitative testing was all the laboratory information a clinician needed to manage an addiction. This assumption can perhaps be traced to the war-on-drugs ideology that considers the fact (i.e., presence) of any illicit drug far more important than how much is used. The primary focus of most current drug abuse testing is accurate detection of minute amounts of drug that can be used against patients in potential legal proceedings, rather than interest in the extremes of drug use.

The dangers of any drug use (legal or illegal) are clearly related to how much of a drug or combination of drugs a person takes. This is the clinical, as opposed to forensic, dimension. Quantitation of drug use measures one aspect of the severity of the addiction the clinician is treating. Combined with the information available from history and physical examination, quantitation has the potential of improving a clinician's ability to manage severe drug or

polydrug use and, in the pharmacotherapy of narcotic addicts, to safely administer methadone or other medications in substance abusing patients.

The research on quantitated urine drug testing is limited. Kell (1992b) has reported use of quantitated urine methadone levels in conjunction with a computerized pharmacokinetic program to generate a calculated methadone blood level within 5% to 10% of measured serum values measured by fluorescence polarization immunoassay (FPIA) or gas chromatography-mass spectrometry (GCMS). Quantitated urine levels of methadone were also reported to help detect methadone supplementation or diversion. Kell (1992a) also reported relatively predictable levels of urinary diazepam and alprazolam excretion that allows estimation of amounts of illicit use, or compliance with therapeutically prescribed medications. Tennant (1990) discussed the therapeutic value of sequential quantitative urine testing in monitoring gradual drug washout, as well as documenting and even predicting relapse based on falling levels of drug in the urine. Both Kell and Tennant have used FPIA technology on-site in substance abuse treatment programs with methadone components. Batki and colleagues (1993)

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recently reported the use of quantitated urine drug levels using high-pressure liquid chromatography (HPLC) methodology to document reductions in cocaine levels in fluoxetine-treated patients, which qualitative testing failed to demonstrate. These preliminary investigations have pointed the direction for further studies of clinical uses of quantitative drug testing.

In this report, urine drug-level data is presented with a view to establishing *ranges of positivity* and eventual guidelines for interpretation of quantitative results. Case examples demonstrate clinical uses of quantitative data in the evaluation and management of a variety of addiction problems. In addition, the clinical uses of on-site laboratory services in the outpatient management of the spectrum of polydrug abuse typical of large methadone programs are illustrated.

METHODS

Using on-site FPIA technology (Abbott ADX and TDX), all patients admitted either to Bi-Valley Medical Clinic's 21-day Medically Supervised Opioid Withdrawal Program (MSW) or to methadone maintenance have quantitated urine drug screens run on early morning urine specimens given on the day of admission. The ADX allows rapid multidrug screens on a single sample. On-site laboratory services allow the medical staff access to quantitated test results prior to making admission-dosing decisions, rather than obtaining results from a reference laboratory days later when they are of much less medical value. The ADX is also used for immediate analysis of specimens ordered on patients with special clinical situations. Finally, all patients on methadone maintenance have one screen per month run on the TDX batch analyzer, providing the clinical staff with quantitated drug levels on all patients. Positive tests from these different clinical situations provide the data reported in this study.

Routine screens are run for amphetamine/dextroamphetamine, opioids, cocaine, and benzodiazepines (BZs). BZs are monitored because of their frequent licit and illicit use by opioid-dependent patients and because of the special toxicity that may exist when methadone is combined with abuse of BZs. Malcolm and colleagues (1993) reported that diazepam is the preferred BZ among substance users and that cocaine and opioid addicts are six times more likely to use diazepam than other BZs. Methadone was monitored on a time-limited research basis to assess ranges and levels of urinary methadone under conditions of routine medical dosing and to assess whether, as Kell has described, quantitative levels can be used to detect non-compliance with dosing (i.e., augmenting doses or diverting).

Early in using this technology it became apparent that the ranges of the assays available for the ADX and TDX were inadequate to the task of measuring the very high urine

drug levels seen in Bi-Valley Medical Clinic's population and that dilution and retesting specimens were routinely required to fully quantitate the results. The ranges for the Abbott reagents are: opioids 1,000 ng, benzoylecgonine 5,000 ng, amphetamine/methamphetamine 8,000 ng, BZ 2,400 ng, and methadone 4,000 ng. Samples with levels above these ranges must be diluted and reanalyzed. As can be seen, the opioid assay is the most problematic, requiring dilutions in 86% of positive tests. Assays are reported as positive only when they exceed the recommended thresholds (Abbott Laboratories 1993): 300 ng for cocaine and amphetamine, 200 ng for opioids and BZs, and 250 ng for methadone.

Given the narrow range of the Abbott opioid reagent (1,000 ng) and the economic need to minimize the number of retests, a dilution protocol was adopted whereby positive opioid tests beyond the 1,000 ng reagent limit were immediately diluted to 1:64 and retested. This first dilution identifies positives in the 1,000-64,000 ng range. Samples higher than 64,000 ng were then diluted 1:8 again, extending the range to 512,000 ng (i.e., 1:512 dilution) and retested. Ten percent of the total opioid-positive tests needed dilutions of 1:512. The other assays, while less problematic by virtue of their wider assay range, all required similar dilution procedures. Most of the data reported reflects a manual dilution protocol, using Eppendorf (buffer) and Oxford (sample) pipettes. The need for increased speed and accuracy in the technical process leads to the change from manual to an automated pipetter/diluter system (Hamilton Microlab 500). Some of the most recent data in the sample reflects use of this automated system.

Sample dilution increases the inaccuracy of this methodology. At the highest dilution used (1:512), within-run variability for opioids was 15%. This estimate was achieved by running a sample that required a 1:512 dilution 10 times, resulting in an average of 96,358 ng/ml \pm 14,336. A similar analysis of a 1:512 diluted cocaine specimen yielded a 9% variability, 232,256 ng/ml \pm 21,248. Within-run variability for specimens within range of the Abbott assays is under 5% (Abbott Laboratories 1993). The highest dilution (1:512) appears to introduce roughly a 5% to 10% increased variability, which may not, however, be so great as to invalidate the clinical use of what might be best referred to as "high ranges" of positivity. Developing assays with wider ranges will be important to reduce this variability and to reduce costs of retesting. Unless specifically stated, all results reported here are unconfirmed by a different methodology, although the majority of positive tests required repeat FPIA testing of diluted specimens. The documented accuracy of immunoassays (Abbott Laboratories 1993; Cone & Weddington 1989; Polkis 1987) and the purely medical uses of the results made such testing unnecessary and too costly as a routine procedure. How-

TABLE I

DATA FOR 3,477 POSITIVE DRUG ASSAYS FOR THE FIVE DRUG CLASSES

	Opioids	Benzodiazepine	Methadone	Cocaine	Amphetamine
Observations	1626	687	401	416	347
Median Value	9152	696	3793	18568	8936
Maximum Value	684032	50816	74816	1970464	509568
Mean Value	28687	1760	7324	81371	40812
Standard Deviation	54334	3546	8130	191939	78150

ever, an important point needs to be understood about immunoassays and quantitation. This technology is by nature semiquantitative since the numerical test result generated is an interpolation from a nonlinear curve. Furthermore, immunoassays are not purely specific for a single substance due to some cross-reactivity with chemically related substances (Baselt 1989). Further research is needed to establish the relative accuracy of diluted specimens using FPIA technology or other immunoassays compared to GCMS or HPLC (Baselt 1989).

No attempt was made in this preliminary study to correct for differences in specimen concentration or variables effecting drug excretion. Kell (1992b) attempted to correct for such variables by normalizing urine concentrations to 1.030 and by factoring pH, creatinine clearance, body weight, and sex into a pharmacokinetic profile. Batki and associates (1993) normalized the quantitative results by dividing cocaine concentrations in the urine by creatinine concentrations in the urine, with adjusted concentrations of cocaine metabolite being reported as nanograms of cocaine per milligram of creatinine. Such procedures will certainly help narrow some of the innate variability of the urine data. While many factors affect urinary drug levels, this is little different from many other medical situations where single test results must be interpreted in conjunction with other data. The purpose of this article is to report only uncorrected data that may serve as a baseline for future research.

RESULTS

Table I displays the medians, maximums, means, and standard deviation data for 3,477 positive drug assays for the five drug classes. Figure 1 shows the rank ordered distribution of the same data by type of drug and drug level. The X axis shows each sample from 1 through N, ordered by the amount of drug measured (i.e., sample 1 had the lowest level and sample N the highest). The Y axis shows drug levels in ng/ml. There is one curve for each drug. The N for each is: opioids (N=1626), amphetamines (N=347), cocaine (N=416), BZs (N=687), and methadone (N=401).

The purpose of the figure is to graphically illustrate the range of positivity for each drug; it is not intended to depict a relationship between the different drugs. The five drugs are placed on the same graph to condense the presentation.

The data document a wide range of urine drug levels in a methadone treatment population, a range missed by reliance on qualitative testing. While the number of samples is small, the sharp J-shaped curves may be identifying a clinically important population of users. While sampling time is a significant variable in interpreting quantitative data, it may be that the extremes of the graph represent unusually high levels of use identified at peak excretion points, identifying both the most serious addictions and patients at risk for the most serious acute toxicity. The standard deviations listed in Table I demonstrate the extreme range of the data, but have the further potential of identifying standardized "panic values" for extremely high samples (e.g., two standard deviations from the mean identifies the extreme of positivity).

The highest drug levels are seen with cocaine, where mean levels are 81,371 ng with a maximum level of 1,970,464 ng. BZ levels are perhaps the most difficult to interpret because of the number of different BZs and different strengths potentially present (e.g., diazepam, alprazolam, clonazepam, flurazepam). Many of these BZ tests represent therapeutic drug monitoring done on a sample of methadone maintenance patients prescribed diazepam or clonazepam therapeutically for seizures or anxiety disorders. No attempt was made to factor out which patients' BZ use was illicit. Most illicit BZ use, but certainly not all, seems to reflect relatively low-level diazepam use. The methadone levels are all, with one notable exception to be discussed, reflective of therapeutic doses of methadone in a clinic setting with an average methadone dose of 65 mg and a range of doses to 140 mg, depending on individual patient needs as established by blood level determinations.

Polydrug use in applicants to methadone treatment demands special clinical attention to issues of drug interactions and to the potential for polydrug use to confuse the

Figure 1. Rank Ordered Distribution Of Drug Levels

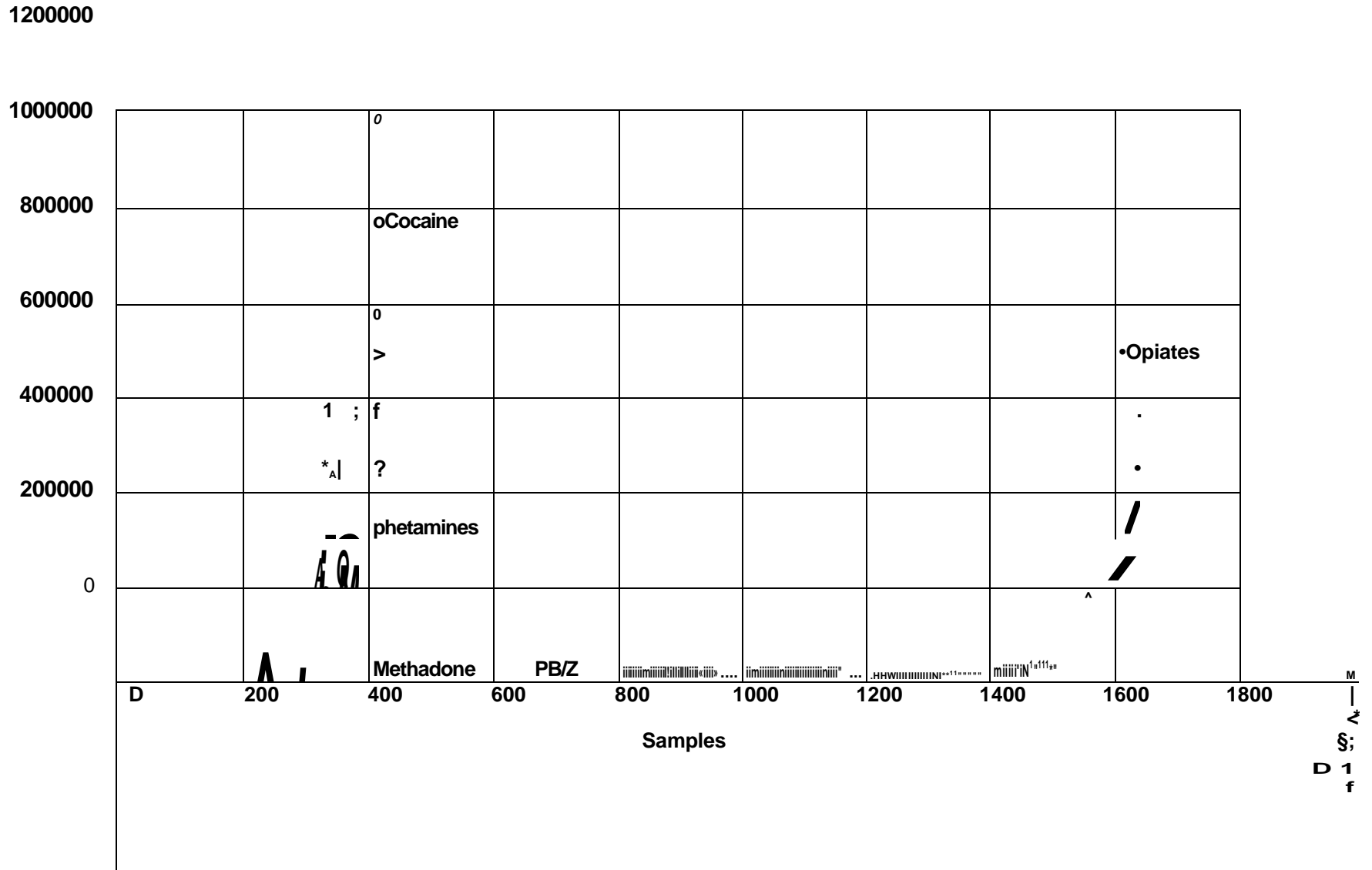


TABLE II
CASE ILLUSTRATIONS

Patient	Date	Opioid	Amphetamine	Cocaine	Benzodiazepine	Methamphetamine
Example 1	3/02/93	45,824		1,970,464	1,001	
	3/02/93					
Example 2	4/15/93	64,512	4,008	87,616	2,161	
Example 3	1/21/93	6,816		465,290		
	2/16/93	153,600		518,144	1,744	
	4/19/93	13,952		75,392		
	4/27/93	15,552		1,901,056	1,337	
	5/03/93	70,656		34,752	210	
	5/13/93	15,104		365,056	670	
Example 4	8/12/93	136,704			12,776	
	8/17/93	96,768			18,976	
	8/20/93	118,784			6,760	
	8/26/93	212,344			1,323	
	8/27/93	41,644			772	
	9/02/93	80,896			445	
	9/07/93	8,704			303	
	9/09/93	4,672			280	
	9/10/93	704			186	
	9/16/93	118			164	
Example 5	2/02/93				151	
	4/06/93				60	
Example 6	6/25/93	295,626				
	7/14/93	153,974				
	7/23/93	287,645				
	7/29/93	890				
	8/06/93	322				
	8/13/93	330				
	8/20/93	0				
Example 7	4/12/93	1,536	209,984		7,500	
	4/13/93		35,392			
Example 8	8/17/93					74,816
Example 9	3/24/93					215
	4/06/93					98
	4/07/93					181
	4/17/93					197

diagnostic picture of opioid withdrawal. Samples from 100 consecutive Sacramento-area patients applying to the 21-day withdrawal (MSW) treatment for opioid addicts are presented to demonstrate the degree of polydrug use complicating admission medical evaluations. Fifty percent of patients were using only opioids, 36% were positive for two drugs, 13% were positive for three drugs, and 1% was positive for four drugs. Fifteen percent of patients were positive for amphetamines on the day of admission and 24% were positive for cocaine. Twenty two percent were using BZs on admission, most unprescribed. Six patients had positive methadone assays. Five patients were on prescribed

methadone during hospitalization or incarceration prior to admission. One had access to methadone from a pain patient.

Table II displays quantitated laboratory data from individual patients to demonstrate how an on-site laboratory is used in conjunction with medical assessment and counseling interventions to manage common clinical situations. While the meaning of a single quantitative test may be difficult to assess, sequential quantitative testing frequently clarifies the interpretation. Clinical situations illustrated are (1) preinduction screening of all admissions to methadone treatment for toxic drug or multidrug levels,

(2) monitoring drug washout during withdrawal regimens, (3) monitoring pregnant women for high drug levels that pose special dangers to the fetus, and (4) monitoring therapeutic compliance with prescribed regimens of abusable medications.

The patient in example 1 presented to the 21-day withdrawal program in apparently severe opioid withdrawal by physical exam. While admitting opioid use, she denied cocaine use. The initial opioid screen was positive at 45,824 ng. Cocaine results were positive but required dilutions and serial testing, so the results were not available before the first half dose of methadone (in this case 20 mg) had been administered. The patient was seen to be sedated within a few minutes of receiving this dose and staff ordered a repeat stat urine opioid screen that documented a much higher opioid level of 144,384 ng. The cocaine result was then reported at 1,970,464 ng.

The patient was presented with these test results and admitted to using heroin in the clinic rest room after the physical exam was completed because "she felt so bad." The cocaine results were so high that medical staff realized that serious cocaine intoxication was responsible for exaggerating physical characteristics of opioid withdrawal (e.g., increased blood pressure, heart rate, dilated pupils, anxiety, and tremulousness). On-site laboratory services provided important support for medical staff in the acute diagnosis and management of this patient. Further methadone dosing was withheld and the treatment plan was altered based on laboratory data documenting severe cocaine abuse, as well as dangerous behavior compromising the safety of outpatient treatment.

This 1,970,464 ng cocaine level was the highest level this clinic laboratory had documented. The specimen was also sent to a reference laboratory for GCMS confirmation. The results were confirmed at 1,280,000 ng. Some of the variation is surely due to the inherent inaccuracy introduced by serial dilutions, especially using a manual pipetter. One other unconfirmed cocaine specimen was seen and analyzed by FPIA at 1,901,056 ng (see example 3 below). Both of these specimens were analyzed before the use of the automated diluter/pipetter. But this discrepancy does support Baselt's (1989) caution concerning limits of quantitation using immunoassays. However, since documentation of the unusually high range is reliable, such data is still very helpful clinically.

Example 2 illustrates the problem of polydrug use complicating the admission to methadone treatment. This patient admitted only recent opioid use but the admission drug screen was positive for four drugs, with moderate levels of cocaine (87,616 ng) and opioid (64,512 ng) coupled with lower levels of BZ (2,161 ng) and amphetamine (4,008 ng). The patient admitted to lying because of fear of not being admitted into methadone treatment (a common reason given for not reporting polydrug use). He was perceived to be in opioid withdrawal, with no signs of BZ toxicity. However,

the initial dose of methadone was reduced as a safety precaution. This patient was warned about the danger of multiple drug ingestion and the medical staff set up a special urine screening plan to monitor this patient more carefully. The BZ was identified by the patient as diazepam, and based on Kelt's histogram suggested around 20 mg a day of recent use, a level he admitted to using in the few days before admission.

Example 3 shows another patient with very high levels of polydrug use, especially cocaine. Opioid use persisted at low to moderate levels, but cocaine use increased to as high as 1,901,056 ng. In addition, the patient began BZ use to counteract stimulant side effects. Clinical interventions were not effective in altering this use. He reported that friends gave him drugs in return for favors. Dealing or other criminal activity seemed a more likely explanation of his being able to afford continuous high-level polydrug use. He abruptly left treatment as the program made increased demands for participation. Quantitation identified consistently high levels of polydrug use, suggesting that drug dealing might be occurring.

Tennant (1990) demonstrated how low-level episodic drug use occurs without physical dependence, and drug elimination occurs rapidly without withdrawal syndromes. The situation with high levels of compulsive (addictive) use is clinically quite different, with longer washout periods during which qualitative tests remain positive as levels are falling, and during which withdrawal syndromes emerge that often result in relapse. If the patient is not as impaired as the high levels might indicate, then one can also infer the presence of tolerance. In example 4, a routine urine on an established maintenance patient showed 12,776 ng of BZ (identified by the patient as diazepam) as well as 136,704 ng of opioid, reflecting heroin use. There was mild impairment, indicating tolerance to both drugs and intensive clinical monitoring and urine testing were initiated. However, five days later the patient presented with gross intoxication and a stat urine showed a much higher level of 18,976 ng of BZ as well as high levels of opioid. The patient admitted to a sudden escalation of diazepam use, ingesting one hundred 10 mg diazepam tablets (i.e., 1,000 mg) in the prior 24 hours. She was placed on almost daily urine opioid and BZ testing and daily clinical monitoring. Urine diazepam levels fell consistently over a four-week period, confirming the patient's denial of any further use. One month after this overdose there were still traces of BZ in the urine. Relapse into diazepam use would have been detected as increased urinary levels, which did not occur. Interestingly, only mild BZ withdrawal symptoms emerged, not requiring medication. Opioid use continued, but these levels also began to fall, confirming the patient's report of less heroin use.

Example 5 illustrates clinical monitoring of a patient on clonazepam (3 mg/day) for panic and post-traumatic stress symptoms. Urinary levels of 114 ng and 145 ng are

below the 200 ng threshold, but not below the 40 ng sensitivity of the Abbott assay. Although the BZ assay is nonspecific, the very low but detectable levels of clonazepam in the urine allow clinicians to monitor compliance with therapeutic regimens of this medication. For the same reason, clonazepam can be a useful medication to manage outpatient BZ withdrawal since therapeutic doses of 1 to 4 mg a day produce levels usually under 200 ng. Illicit use of BZs, especially diazepam, can be detected by urinary levels much higher than clonazepam produces.

Example 6 demonstrates the value of routine quantitative screening of pregnant methadone maintenance treatment patients in documenting high levels of drug use. This patient was four months pregnant when the first opioid level was reported at 295,626 ng. It was not clinically apparent that this patient's use was unusually high. When shown the quantitative results, the patient reported heroin use two to three times a day. Subsequent tests documented high levels as counseling interventions focused on major stresses in her life and medical interventions focused on having close obstetrical monitoring for signs of fetal distress. The tests in the second month of treatment showed dramatic reductions in drug levels to 890, 322, and 330 ng. Qualitative testing with a 200 ng threshold would have reported all three tests as positive and missed the major improvement that led to the negative test on August 20, 1993.

Example 7 illustrates the use of quantitation in monitoring patient compliance with prescribed regimens of stimulants. During admission to the MSW program, this patient reported being treated by a neurologist for narcolepsy and presented a current prescription for dextroamphetamine (60 nig/day) and flurazepam (60 mg h.s.). The preadmission urinary amphetamine level came back at 209,984 ng. When confronted with what appeared to be high levels, the patient admitted to overuse of medications so he would not oversleep his 7:00 a.m. appointment. The BZ level of 7,500 ng seemed, from very limited experience with urine levels of flurazepam, to be consistent with a 60 mg dose. Considering the patient's tolerance to daily prescribed amphetamines and the clinical picture of moderate to severe narcotic withdrawal, the medical staff admitted this patient to the program with a plan to repeat amphetamine testing on the next day. The level was reported as 35,392 ng, perhaps indicating early compliance with treatment. While very preliminary, this case suggests that patients on prescription stimulants, for legitimate disorders, might also be monitored for compliance using urinary assays, as Kell has reported for methadone and diazepam. It is also possible that compliance with prescription opioids could be monitored once normative values for different medications were established.

Example 8 demonstrates the value of quantitative methadone levels in identifying a patient supplementing clinic methadone with street methadone. This patient com-

plained of not stabilizing on methadone and his dose was gradually increased to 90 mg. The urine level of 74,816 ng was higher than anything previously seen, but it was very early in the study. The more methadone levels that were examined the more unusual this result appeared: it was 50% higher than the second highest level in the sample of 401 assays. When the patient was asked to help explain this result, he reported at that time using 90 mg of methadone in pill form in addition to 90 mg from the clinic. Kell (1992a) reported that individual patient profiles for methadone excretion can be established, which would allow detection of supplementing of daily clinic dose with street methadone. This case supports the possibility. Qualitative testing for methadone and metabolite are not helpful in this kind of discrimination.

California regulations mandate that all patients must have qualitative testing for methadone and metabolite performed at a state-approved high-complexity reference laboratory. This testing is most often done by thin layer chromatography (TLC), which has a positivity threshold of 2,000 ng for methadone and 1,000 ng for the metabolite. Example 9 documents a patient maintained on 45 mg of methadone who occasionally would be reported as having no methadone and no metabolite, bringing a regulatory presumption that he was diverting methadone since he was on take-home medications. Five consecutive specimens obtained from this patient over a three-week period fell at or below 215 ng, well below the reportable range for TLC. Patients on low doses or those who metabolize methadone rapidly are frequently accused of diverting methadone because their levels fall below these TLC thresholds. Twenty-five percent of the study's methadone assays (N=401) fell below this 1,000 ng reporting level. The reference laboratory clearly reports levels well below these published thresholds since no methadone results are not that common. However, quantitative immunoassays with sensitivity in the 50 ng range can minimize problems associated with such false-negative qualitative screening and false accusations of compliant patients. Further research is needed to verify Kell's observation that quantitated urine methadone levels can replace costly methadone metabolite testing as a way of monitoring for diversion.

DISCUSSION

While recognizing the preliminary nature of the data and the complicated issues involved in their interpretation, quantitative urine drug levels appear to be a valuable adjunct to addiction treatment services, bringing a new level of objectivity to medical decisions. The ability to track drug levels sequentially and to detect extremes of drug use represents a significant advantage over mere qualitative testing. Furthermore, patients respond more positively to such feedback and are more likely to understand and accept medical decisions based on safety when presented with

quantitated information. An on-site laboratory's ability to provide timely information adds further to the clinical value of quantitation.

This report documents a remarkable frequency of high urinary drug levels. Fatalities have been reported at lower urine concentrations of cocaine, amphetamines, and opioids than reported here. Baselt (1982) reported on 18 cocaine fatalities with a urine range of 1,400 to 215,000 ng/ml (mean 47,000 ng). In the present study, the mean cocaine level was 81,371 ng. Baselt reviewed one fatal methamphetamine overdose with a 320,000 ng urine level; the present study's range extended to 509,568 ng. The range of opioid positivity in ten morphine fatalities was 14,000 to 81,000 ng (mean 52,000 ng). The present study's mean opioid levels were 28,687 ng, with a range to 684,032 ng. While lethal doses for drugs of abuse are quite variable, with deaths occurring at low and high levels, heavier and more frequent users are more likely to experience a variety of adverse reactions. There were no fatalities or acute hospitalizations in patients with the highest drug levels, reflective of remarkable tolerance. In some cases the laboratory data confirmed toxicity that was already apparent clinically. However in many other cases, because of tolerance, quantitative levels were the first indication of high levels of drug use.

BZs are readily available on the street and pose special dangers when combined with opioids or other sedative drugs. Routine BZ screening of patients has been very valuable in identifying and tracking addictive use of these medications. The consistency of sequential urinary BZ levels has also allowed clinicians to safely manage BZ withdrawal in the outpatient setting and identify relapse quickly when it occurs. Therapeutic BZs can be monitored for compliance, since stable doses of individual BZs appear to give relatively consistent urinary levels. Based on current experience with BZ monitoring, the potential seems to exist to also monitor compliance with therapeutic regimens of opioids and stimulants through quantitative urine assays.

Batki and colleagues (1993) reported the use of quan-

titated urine drug levels as a more sensitive measure of treatment outcome than simple qualitative testing. The failure of the War on Drugs and expectations of total abstinence to reduce the social problems of drug use has led to increasing public health acceptance of harm-reduction strategies that aim at gradually reducing high-risk behaviors in the context of continued drug use. Quantitated drug levels have the potential of measuring the gradual effects of a sequence of harm-reduction interventions (e.g., street outreach efforts, needle exchange or pharmacologic interventions), documenting subtle changes that qualitative testing might miss.

This study stretches the limits of immunoassay technology. FPIA is a unique tool, being more cost-effective and less technologically demanding than other methods of quantitation. Small on-site laboratories can therefore provide highly accurate quantitative results within the range of standard assays. How FPIA compares with HPLC or GCMS in measuring the high drug concentrations characteristic of this study, beyond the range of standard assays, is a matter for further research.

The accuracy of FPIA technology could obviate the need in the medical setting for routine, costly confirmation testing of all positive tests. If a patient or staff questions a particular result, the sample can be reanalyzed by a different method at that point. This could save programs thousands of treatment dollars now spent on routine confirmation tests.

FPIA technology is categorized as a moderate complexity test under the Clinical Laboratory Improvement Act (CLIA 88), which established national standards and provided classification and regulatory oversight for clinical laboratories. Regulations should be modified to support on-site clinical testing in methadone programs. On-site testing combined with quantitative analysis has the potential to improve the safety and effectiveness of methadone or other pharmacotherapies in the management of narcotic addiction.

REFERENCES

- Abbott Laboratories. 1993. TDx FLx Assay Manuals. North Chicago, Illinois: Abbott Laboratories.
- Baselt, R.C. 1989. Inappropriate use of immunoassays as a quantitative tool. *Journal of Analytical Toxicology* 13:1. Baselt, R.C. 1982. *Disposition of Toxic Drugs and Chemicals in Man*. Davis, California: Biomedical Publications.
- Baselt, R.C. 1980. *Analytical Procedures for Therapeutic Drug Monitoring and Emergency Toxicology*. Davis, California: Biomedical Publications.
- Batki, S.L.; Manfredi, L.B.; Jacob, P. & Jones, R.T. 1993. Fluoxetine for cocaine dependence in methadone maintenance: Quantitative plasma and urine cocaine/benzoylcegonine concentrations. *Journal of Clinical Psychopharmacology* 13 (4): 243-50.
- Cone, E.J. & Weddington, W.W. 1989. Prolonged occurrence of cocaine in human saliva and urine after chronic use. *Journal of Analytical Toxicology* 13:65.
- Kell, M.J. 1992a. Methadone plasma levels determined from spot urine collections. *ASAM Abstracts* 17A and 18 A: 179-180.
- Kelt, M.J. 1992b. Therapeutic drug monitoring using rapid, computerized quantitative urine monitoring. *ASAM Abstract* 19A:180-181.
- Malcolm, R.; Brady, K.T.; Johnston, A.L. & Cunningham, M. 1993. Types of benzodiazepines abused by chemically dependent inpatients. *Journal of Psychoactive Drugs* 25 (4): 315-19.
- Polkis, A. 1987. Evaluation of TDx cocaine metabolite assay. *Journal of Analytical Toxicology* 11:228.
- Tennant, F.S. 1990. Quantitative urine levels of abusable drugs for clinical purposes. *Clinics in Laboratory Medicine* 10 (2): 301-9.