

ORIGINAL ARTICLE

Using an algorithm applied to urine drug screening to assess adherence to a hydrocodone regimen

J. E. Couto* PharmD MBA, L. Webster† MD FACPM FASAM, M. C. Romney* RN MS JD MPH, H. L. Leider‡ MD MBA and A. Linden§ DrPH MS

*Jefferson School of Population Health, Thomas Jefferson University, Philadelphia, PA, †Lifetree Clinical Research and Lifetree Pain Clinical, Lifetree Medical Inc., Salt Lake City, UT, ‡Ameritox Ltd., Baltimore, MD, and §Linden Consulting Group, Hillsboro, OR, USA

SUMMARY

What is known and objective: This study examined the ability of an algorithm applied to urine drug levels of hydrocodone in healthy adult volunteers to differentiate among low, medium and high doses of hydrocodone.

Methods: Twenty healthy volunteers received 20, 60 and 120 mg daily doses of hydrocodone dosed to steady-state at each level while under a naltrexone blockade. Using a fluorescence polarization immunoassay (FPIA), two urine samples were taken at each dosing level from each participant once steady-state was reached. The concordance was calculated for raw and adjusted FPIA urine hydrocodone values within each study participant across all doses. An analysis of medians was calculated for each of the dosage groupings using Bonett-Price confidence intervals for both raw and adjusted FPIA values. Finally, the Somers' D rank order analysis was performed for both raw and adjusted FPIA methods followed by a linear comparison of parameters to further determine which lab value reporting method produced a better fit with dosage.

Results and discussion: The concordance correlation coefficient for the pairs of raw urine FPIA values was 0.339, while the concordance correlation coefficient for the pairs of normalized FPIA values using the algorithm was 0.677. While some overlap of the confidence intervals was observed using the raw FPIA values, the intervals for the

adjusted FPIA levels did not overlap between any dose levels, despite the application of a Bonferroni adjustment to correct for multiple comparisons. Results of the Somers' D analyses suggest that the adjusted FPIA method is 15% more likely to be concordant with dose than the raw value method.

What is new and conclusions: In contrast to raw FPIA values, an algorithm that normalizes hydrocodone urine drug levels for PH, specific gravity and lean body mass discriminates well between all three of the daily doses of hydrocodone tested (20, 60 and 120 mg), even when correcting for multiple analyses.

Keywords: algorithm, hydrocodone, medication adherence, urine drug testing

WHAT IS KNOWN AND OBJECTIVE

Hydrocodone is the most prescribed opioid, controlled substance and prescription product in the United States (US). This suggests there is a need for close monitoring of hydrocodone prescribing, dispensing and use to prevent abuse and diversion (1). The US National Forensic Laboratory Information System (NFLIS) reports that diversion and abuse of hydrocodone have been escalating in the last few years. Hydrocodone is the most often identified prescription drug product by state and local laboratories dedicated to analysing substances for law enforcement operations (2). According to the Drug Abuse Warning Network (DAWN), nearly 66 000 emergency department (ED) visits in 2007 were due to the non-medical use of hydrocodone. This figure represents approximately one quarter of all non-medical, opioid-related ED visits in 2007.

Received 29 March 2010, Accepted 17 November 2010

Correspondence: Joseph E. Couto, PharmD MBA, Assistant Professor, Jefferson School of Population Health, Thomas Jefferson University, 1015 Walnut Street, Suite 115, Philadelphia, PA 10107, USA. Tel.: +215 955 1708; fax: +215 503 7598; e-mail: joseph.couto@jefferson.edu

DAWN data also shows that while ED visits represent a 'unique opportunity for healthcare providers to identify and refer patients for appropriate follow-up care', almost 60% of these visits ended with no evidence of follow-up care (3).

Hydrocodone is an effective medication for managing chronic pain in many individuals; however utilization for a legitimate need must be balanced with the high potential for abuse, diversion and supplementation of the drug. Thus monitoring the compliance (i.e. whether patients are taking their medications in a manner consistent with the prescribed dose and frequency) of patients on pain management regimens is an important component of the care of patients on chronic opioid therapy (4). Studies have demonstrated the inaccuracy and unreliability of patient self-reporting alone when compared to laboratory confirmation through urine drug testing (UDT) (5). Therefore, laboratory drug testing has been recognized as a necessary complement to behavioural assessment of patient adherence and compliance with a prescribed pain regimen (5, 6).

While UDT provides important information about whether a patient is taking a chronically prescribed opioid, a 'positive' test result still leaves open the possibility that a patient is misusing or diverting their medication. To address this problem, work conducted in methadone clinic patients in the mid-1990s demonstrated that urine testing utilizing an algorithm that 'normalizes' each patient's UDT results for the effects of urine pH, specific gravity, volume of distribution, and gender can closely approximate a patient's actual plasma methadone concentration (7, 8). This work with methadone patients was later extended to other opioids. The resulting algorithm was then used to compare normalized urine drug levels from patients with measured observed ranges to normalized urine drug levels derived from patients who were known to be taking their medications as prescribed. Patients with 'normalized' urine drug levels above or below the expected ranges were felt to have a significantly higher likelihood of drug non-adherence, misuse, abuse, or diversion.

The current study tests the ability of a proprietary algorithm for hydrocodone to examine discrimination of urine drug concentrations in healthy volunteers between low (20 mg), medium (60 mg) and high (120 mg) doses of hydrocodone.

A similar study using a related oxycodone algorithm was also conducted to explore the utility of this approach when applied to OxyContin[®], an opioid commonly used by physicians treating patients with chronic pain that has a different pharmacokinetic profile than hydrocodone (9).

METHODS

Study design

The current study was a single group, multiple dose study of hydrocodone in healthy adult volunteers. Subjects (Table 1) were 18–36 years of age, had BMIs ranging from 18 to 30 kg/m², and were all non-smokers. Women were required to have a negative urine pregnancy test prior to study initiation and were required to use a medically accepted method of contraception during the duration of the study. All subjects were tested for abnormal substances in the urine. Abnormal urine tests were exclusionary. Subjects were also excluded if they had an abnormal physical exam, ECG, or clinical laboratory tests as evaluated by the investigator. Additional exclusion criteria included: history of significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary or metabolic disease. Any participant having an allergy or history of hypersensitivity to hydrocodone, naltrexone, opioids or similar compounds were excluded. Participants were ineligible for the study if they had used any prescription medications or over-the-counter (OTC) medications including herbal preparations 30 days prior to study initiation. Participants were not allowed to use any prescription or OTC medications during the study that could interfere with the evaluation of study medication. Subjects were forbidden to use alcohol, ingest grapefruit, grapefruit juice, caffeine

Table 1. Characteristics of study participants

| Variable | Data | Mean | SD |
|--------------------------------------|-------|-------|------|
| Number of subjects | 20 | | |
| Female subjects | 3 | | |
| Age (in years) | 18–36 | 23.6 | 4.2 |
| Height (in inches) | | 70.5 | 3.0 |
| Weight (in lbs) | | 178.1 | 31.6 |
| Body mass index (kg/m ²) | 18–30 | 25.0 | 3.0 |

or xanthene-containing products 48 h before dosing and during the dosing periods. All subjects were screened for any major phenotypic variation of the CYP2D6 enzymes using a commercially available screening test (PGXL Laboratories, Louisville, KY, USA) and poor, rapid, and ultrarapid metabolizers were excluded from the study.

The study had two parts. In Part 1, three healthy volunteers (three white males) underwent naltrexone dosing and evaluation. These subjects ranged in age from 22 to 26 years and averaged 70 inches in height and 177 pounds in weight. The purpose was to assess whether naltrexone would interfere with the urine analysis of hydrocodone. In Part 2, 20 healthy volunteers (3 females and 17 males) each received escalating doses of hydrocodone and fixed doses of naltrexone according to the study protocol. These subjects ranged in age from 18 to 36 years (mean = 23.58) and averaged 70.5 inches in height and 178 pounds in weight. Four participants were of Asian descent, and the remaining 16 were Caucasian. Four subjects in Part 2 took concomitant medications, with two using nutritional supplements and two using birth control.

The volunteers received 20, 60 and 120 mg daily doses of hydrocodone dosed to steady-state at each level. Two urine samples were collected at each dose level, at times approximating steady-state peak and trough hydrocodone plasma concentrations. Urine opioid concentrations were adjusted by a proprietary algorithm accounting for lean body weight (LBW), pH and specific gravity.

Oral hydrocodone was compounded as a single entity in doses of 5 and 10 mg capsules. Dosing intervals were 5 mg q 6 h for six doses, 15 mg q 6 h for six doses and 30 mg q 6 h for six doses (Table 2). Naltrexone was given approximately 12 h

before the first hydrocodone dose and every 12 h while on the study.

Analytic approach

The current study assessed how well an algorithm that adjusted or 'normalized' standard urine drug levels (e.g. raw levels), obtained by fluorescence polarization immunoassay (FPIA), for urine pH, urine specific gravity, lean body weight, and gender discriminated between the three different doses of hydrocodone (20, 60 and 120 mg/day).

First, data was tested for the concordance (10, 11) between each pair of raw and adjusted FPIA values for each study participant across all doses. The rationale for this was 2-fold: (i) to determine if indeed participants achieved steady-state at each drug dose, and (ii) to assess which of the two methods (raw or adjusted FPIA) achieved better concordance. In the case of the former, whether a patient achieves steady-state is of clinical importance because during the accumulation phase, inter-patient variability in elimination and accumulation can have exaggerated effects on observed serum and urine levels. In the case of the latter, it can be hypothesized that the method which achieves better concordance is also likely to show better discrimination between doses, as a direct result of lowered variability within each dose.

Second, an analysis was conducted of medians for each of the dosage groupings using Bonett-Price confidence intervals (12–14) for both raw and adjusted FPIA values. In this study, an analysis of medians is a more appropriate choice than an analysis of means, given that (i) the distribution of values in this relatively small sample appears skewed at each dose level (see Figs 1 and 2), (ii)

Table 2. Participant dosing schedule per protocol

| | Naltrexone | Hydrocodone 5 mg | Hydrocodone 15 mg | Hydrocodone 30 mg |
|--------------|--------------------|---------------------|------------------------|----------------------|
| Day and time | | | | |
| 0 | 1800 | | | |
| 1 | 0600, 1800 | 0700, 1300, 1900 | | |
| 2 | 0600, 1800 | 0100, 0700, 1300 | 1900 | |
| 3 | 0600, 1800 | | 0100, 0700, 1300, 1900 | |
| 4 | 0600, 1800 | | 0100 | 0700, 1300, 1900 |
| 5 | 0600, 1800 | | | 0100, 0700, 1300 |
| 6 | Release from study | | | |

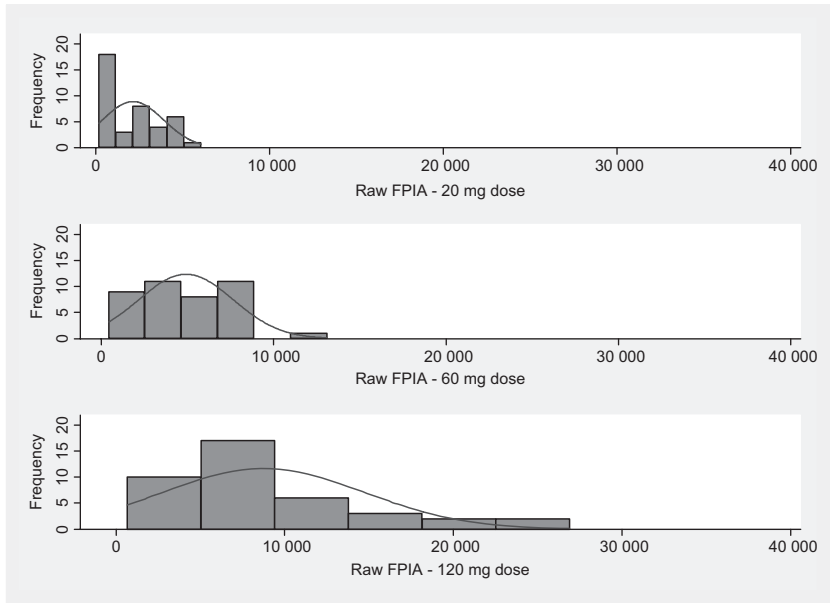


Fig. 1. Distribution of raw florescence polarization immunoassay (FPIA) values (in ng/mL) by dose.

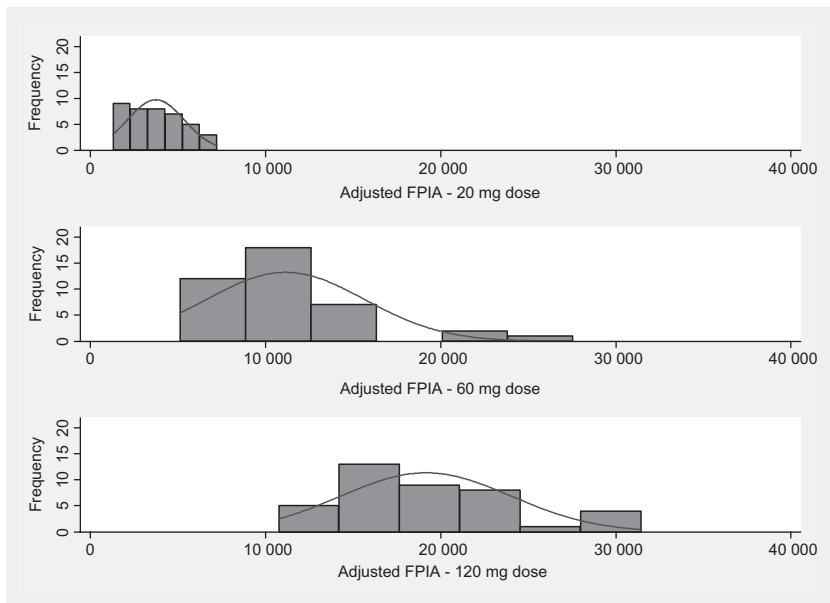


Fig. 2. Distribution of adjusted florescence polarization immunoassay (FPIA) values (in ng/mL) by dose.

there is no information as to the true population distribution of the raw or normalized FPIA values and (iii) the analysis of medians is robust to almost any type of non-normality that would likely be encountered in practice. The Bonett-Price confidence interval method was chosen in particular because of its superior performance in simulation experiments of small samples (12). In order to establish even more conservative estimates, a Bonferroni adjustment was applied to the confidence intervals.

Third, we tested which of the two methods (raw or adjusted) achieved better concordance with dose, using the Somers' D rank order analysis followed by a linear comparison of parameters from the two models (15, 16). More specifically, the Somers' D statistic was used to indicate the probability that lab values (whether raw or adjusted) increase with increasing dose more so than decrease with increasing dose. To determine which of the two methods (raw or adjusted) better predicted dose, the difference between the two

parameter estimates was tested using a linear comparison model. To allow for dependencies between repeated measures on the same patient, all analyses were performed clustering by patient.

All statistical analyses were conducted using STATA (version 10.1) software (Statacorp, College Station, TX, USA). Concordance was estimated using 'concord', a user written program for STATA by Thomas J. Steichen & Nick J. Cox (17, 18). Pair-plots (Figs 3 and 4) were created using 'pairplot' a user-written program for STATA by Nick J. Cox (19). Bonett-Price confidence intervals were estimated using 'bpmedian', a user written program for STATA by Roger Newson (20). Von Mises Somers' D statistics were estimated and linear comparisons were

performed using 'somersd', a user written program for STATA by Roger Newson (21).

RESULTS AND DISCUSSION

The concordance correlation coefficient (11) for the raw FPIA values (Table 3) was 0.339, while the concordance correlation coefficient for the normalized FPIA values using the aforementioned algorithm (Table 3) was twice this value at 0.677. The explanation for this discrepancy can be seen in Figs 3 and 4. Figure 3 shows that most pairs of values are skewed toward the first raw FPIA measurement value (as indicated by positive values on the y -axis). This skew becomes more apparent as the mean raw FPIA level increases, with extreme spikes exhibited at the highest raw FPIA levels. Conversely, Fig. 4 illustrates a more uniform distribution of concordance between first and second measurements of adjusted FPIA levels. The few spikes that are found in the data are also at the higher end of the continuum, but do not appear to be biased more toward the first or second adjusted FPIA measurement.

Figures 1 and 2 illustrate the distributions of raw and adjusted FPIA values, respectively, by the daily doses under study. Upon visual inspection, it is clear that none of the doses under either method represent truly normal distributions. Moreover, there is no consistency in the general form among

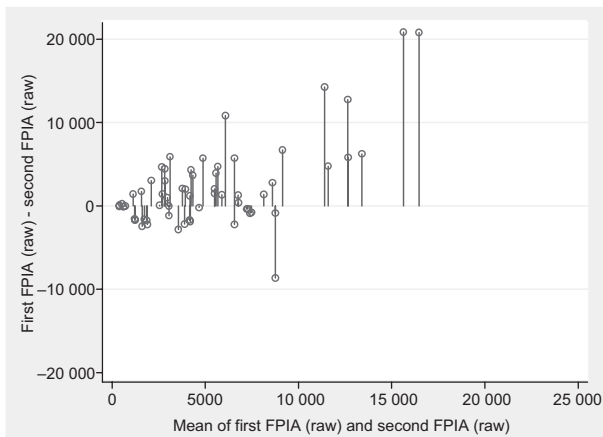


Fig. 3. A plot of difference vs. mean for first and second raw FPIA levels (in ng/mL).

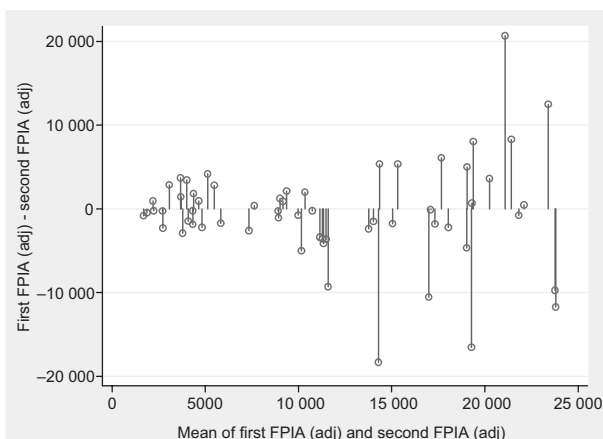


Fig. 4. A plot of difference vs. mean for first and second adjusted FPIA levels (in ng/mL).

Table 3. Median estimates and Bonett-Price 95% confidence intervals for raw and adjusted fluorescence polarization immunoassay (FPIA) values by dose (with and without Bonferroni adjustment)

| Dose per day (mg) | Median | LCI | UCI | Bonferroni adjusted | |
|-------------------|--------|--------|--------|---------------------|--------|
| | | | | LCI | UCI |
| Raw FPIA | | | | | |
| 20 | 2054 | 1076 | 3032 | 859 | 3248 |
| 60 | 4670 | 3230 | 6110 | 2912 | 6429 |
| 120 | 7326 | 5547 | 9106 | 5154 | 9499 |
| Adjusted FPIA | | | | | |
| 20 | 3601 | 2764 | 4437 | 2579 | 4622 |
| 60 | 9620 | 8806 | 10 435 | 8626 | 10 615 |
| 120 | 18 113 | 16 360 | 19 865 | 15 973 | 20 252 |

LCI, lower confidence interval; UCI, upper confidence interval.

the distributions. Estimators of shape parameters, such as skewness and kurtosis coefficients are not reported, because they generally exhibit large sampling variability in small samples and are biased (toward normality) in non-normal distributions (12). These concerns led to the choice of a median analysis using Bonett-Price confidence intervals.

Table 3 presents the median estimates and Bonett-Price 95% confidence intervals for raw and normalized FPIA values by dose, both with and without Bonferroni adjustment. As shown, the confidence intervals for the raw FPIA levels do not overlap between the 20 and 60 mg daily doses but do overlap between the 60 and 120 mg daily doses. In applying the more conservative Bonferroni adjustment, the discrimination between the 20 and 60 mg doses disappears. Conversely, the confidence intervals for the adjusted FPIA levels do not overlap between any dose level, regardless of the application of the Bonferroni adjustment. In other words, the adjusted FPIA method shows excellent discrimination between 20, 60 and 120 mg daily doses of hydrocodone even when conservative adjustments are applied.

The results of the Somers' D analysis indicate that the adjusted FPIA values are 93% more likely to increase with increasing dose than decrease with increasing dose (CI's 88%, 98%, $P < 0.0001$) whereas the raw lab values are 63% more likely to increase with increasing dose than decrease (CI's 52%, 73%, $P < 0.0001$). The linear comparison of the difference between raw and adjusted models indicates that the adjusted model is 15% more likely to be concordant with dose than the raw model (CI's 9%, 22%, $P < 0.0001$).

The current study extends prior work with methadone and oxycodone to hydrocodone, in an environment more structured than the work conducted with methadone (7, 8). The results of this study confirm that, in contrast to raw FPIA values, the proprietary algorithm discriminates well between all three of the daily doses of hydrocodone tested (20, 60 and 120 mg). These results persisted even when conservative confidence intervals were applied. The results of the Somers' D analysis further suggest that the adjusted FPIA method is more likely to be concordant with dose than the raw method. These findings may have important clinical ramifications in the monitoring of pain

management patients by utilizing normalized immunoassay results from urine drug testing.

Much like the previously studied oxycodone algorithm, the hydrocodone algorithm cannot currently be used to determine or predict the specific dose of drug a particular patient is taking. However when combined with observations of aberrant behaviour, structured risk assessments (e.g. ORT, COMM), pill counts, and medical chart reviews, the use of this algorithm should provide additional information that can help clinicians assess the possibility of drug misuse, or non-adherence.

Thus the potential public health implications of this technology are significant, given the widespread problem of prescription drug misuse, abuse and diversion. Urine drug screening typically only confirms the presence or absence of particular substances in a patients' body over a given time period, but offers little insight into whether a patient is likely to be taking the medication as prescribed with respect to total daily dose. Providing clinicians with more specific information regarding their patients' use of medications using this type of algorithm could better inform prescribing decisions. For example, a clinician might take a different approach with a patient complaining of escalating pain with confirmed low levels of the prescribed product in their urine than a patient with confirmed normal levels of the product in their urine. In the setting of a lower than expected urine drug level, where diversion is a consideration, a clinician could choose to institute pill counts, consult a state-wide controlled substance database (if available), or write for smaller quantities of drug over shorter intervals.

Using this technology, clinicians have the opportunity to improve clinical care while reducing abuse and diversion of opioids, however a study to assess the cost-effectiveness of this approach and the economic impact on potential reductions of drug diversion, abuse and misuse would be especially meaningful both to healthcare providers as well as payers. This economic analysis would be especially important in assessing the feasibility of widespread adoption of this technology in lower income countries.

Another potential application of this technology is to apply it to therapies other than pain medications. This concept has yet to be tested, but makes good sense: when medication adherence is

typically suboptimal, clinicians have limited confidence in a patient's report about their medication use, and there is no current physiologic test to assess the response to a drug (e.g. such as cholesterol testing to assess the impact of statin therapy).

It is important to appreciate the limitations of this study when interpreting the results. The current study enrolled healthy volunteers, who took no other concomitant medications 30 days prior to initiation of the protocol. Some patients encountered in the clinical setting use one or more medications that inhibit or induce the CYP2D6 enzymes, which could affect the metabolism of hydrocodone and thus levels detected in the urine. Similarly, volunteers were excluded from the present study if they were determined to be poor, rapid, or ultrarapid CYP2D6 metabolizers. Estimates in the literature state that approximately 7% of White Americans and 2–4% of Black Americans have CYP2D6 drug metabolism phenotypes that classify these individuals as poor metabolizers. Another 2–7% of Caucasians are thought to be rapid or ultrarapid metabolizers of CYP2D6 (22, 23). Thus, while the current study included the majority of CYP2D6 phenotypes that present in US clinics, a small but significant number of phenotypes were excluded. Genetic tests are commercially available to identify individuals with atypical phenotypes whose resulting urine levels of drug metabolites may be chronically low or high based on their particular polymorphism. The generalizability of the results were limited by the small number of subjects and because only three doses were evaluated. However the small sample size was offset somewhat by the repeated sampling of individuals, with a total of 120 data points. Given the fact that patients were perfectly compliant in the current study, a larger trial in a clinic setting is required to define the sensitivity and specificity of the current algorithm with respect to patient adherence. Finally, this study was specific only to hydrocodone, although similar work with oxycodone has been published, and studies with other short and long-acting opioids are ongoing (9). While this technology has meaningful application beyond opioids to support the assessment of medication adherence, the individual, societal, and financial impacts of opioid abuse and diversion presents the most immediate need for this technology.

WHAT IS NEW AND CONCLUSION

The results of the current study point to the fact that urine hydrocodone levels, when adjusted using a proprietary algorithm correlate more closely with the corresponding drug dose than do unadjusted urine hydrocodone levels. When coupled with other clinical data, the information from adjusted urine drug levels should provide insights about medication adherence that extend beyond whether a patient is simply taking any of their prescribed opioid(s). Specifically, the algorithm tested in this study showed promising results when used to differentiate between low and high daily doses of hydrocodone, even when conservative confidence intervals were applied. Additionally, the adjusted method showed better concordance with dose than did the raw method. Although urine testing cannot be used in isolation to identify all patients not following their prescribed opioid regimen nor to predict exactly what dose of opioid a patient is taking in the clinical setting, when coupled with behavioural assessment of patients, it can provide important information to clinicians.

ACKNOWLEDGEMENTS

We would like to thank Roger Newson for his invaluable statistical advice and assistance in using the BPMEDIAN and SOMERSD packages.

CONFLICTS OF INTEREST

Dr Couto is an Assistant Professor and Ms Romney is an Assistant Professor in the Jefferson School of Population Health at Thomas Jefferson University in Philadelphia, PA, USA. Dr Webster is the Director of Lifetree Clinical Research and Lifetree Pain Clinical at Lifetree Medical Inc. in Salt Lake City, UT, USA. Dr Leider is the Chief Medical Officer at Ameritox, Ltd in Baltimore, MD, USA. Dr Linden is the President of the Linden Consulting Group in Hillsboro, OR, USA.

REFERENCES

1. IMS (2009) *U.S. Prescription Drug Sales Grow Slowly; Hydrocodone Most Prescribed*. Available at: <http://seekingalpha.com/article/128003-u-s-prescription->

- drug-sales-grow-slowly-hydrocodone-most-prescribed (accessed 13 July 2009).
- Office of Diversion Control (2008) *National Forensic Laboratory Information System, Midyear Report 2008*. Available at: <http://www.deadiversion.usdoj.gov/nflis/2008midyear.pdf> (accessed 13 July 2009).
 - Substance Abuse & Mental Health Services Administration (2008) *National Estimates from the Drug Abuse Warning Network*. Available at: <http://www.fda.gov/ohrms/dockets/AC/08/slides/2008-4395s1-07-Poneleit.ppt> (accessed 13 July 2009).
 - Chou R, Fanciullo GJ, Fine PG *et al.* (2009) Opioid treatment guidelines: clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Journal of Pain*, **10**, 113–130.
 - Katz N, Fanciullo GJ (2002) Role of urine toxicology testing in the management of chronic opioid therapy. *Clinical Journal of Pain*, **18**, S76–S82.
 - Tellioglu T (2008) The use of urine drug testing to monitor patients receiving chronic opioid therapy for persistent pain conditions. *Medicine and Health, Rhode Island*, **91**, 279–282.
 - Kell MJ (1994) Utilization of plasma and urine methadone concentrations to optimize treatment in maintenance clinics: I. measurement for a clinical setting. *Journal of Addictive Diseases*, **13**, 5–26.
 - Kell MJ (1995) Utilization of plasma and urine methadone concentration measurements to limit narcotics use in methadone maintenance patients: II. generation of plasma concentration response curves. *Journal of Addictive Diseases*, **14**, 85–108.
 - Couto J, Webster L, Romney M *et al.* (2009) Using an algorithm applied to urine drug screening to assess adherence to an OxyContin® regimen. *Journal of Opioid Management*, **5**, 359–364.
 - Lin LI (1989) A concordance correlation coefficient to evaluate reproducibility. *Biometrics*, **45**, 255–268.
 - Lin LIK (2000) A note on the concordance correlation coefficient. *Biometrics*, **56**, 324–325.
 - Bonett DG, Price RM (2002) Statistical inference for a linear function of medians: confidence intervals, hypothesis testing, and sample size requirements. *Psychological Methods*, **7**, 370–383.
 - Price RM, Bonett DG (2001) Estimating the variance of the sample median. *Journal of Statistical Computation and Simulation*, **68**, 295–305.
 - Price RM, Bonett DG (2002) Distribution-free confidence intervals for difference and ratio of medians. *Journal of Statistical Computation and Simulation*, **72**, 119–124.
 - Newson R (2002) Parameters behind “nonparametric” statistics: Kendall’s tau, Somers’ D and median differences. *The Stata Journal*, **2**, 45–64.
 - Newson R (2006) Confidence intervals for rank statistics: Somers’ D and extensions. *The Stata Journal*, **6**, 309–334.
 - Steichen TJ, Cox NJ (1998) Concordance correlation coefficient. *Stata Technical Bulletin*, **43**, 35–39.
 - Steichen TJ, Cox NJ (2008) Software update for concord. *Stata Journal*, **8**, 594.
 - Speaking Stata (2004) *Graphing Agreement and Disagreement*. Statistical Software Components. Available at: <http://ideas.repec.org/cgi-bin/htsearch?q=graphing+agreement+and+disagreement&cmd=Search%21&form=extended&m=all&ps=10&fmt=long&wm=wr&sp=1&sy=1&wf=4BFF&dt=range&db=&de=> (accessed 1 May 2009).
 - BP MEDIAN (2009) *Stata Module to Compute Bonett-Price Confidence Intervals for Medians and Their Contrasts*. Statistical Software Components (SSC). Available at: <http://ideas.repec.org/cgi-bin/htsearch?q=bpmedian%3A+&cmd=Search%21> (accessed 3 June 2009).
 - SOMERSD (2009) *Stata Module to Calculate Kendall’s tau-a, Somers’ D and Median Differences*. Statistical Software Components (SSC). Available at: <http://ideas.repec.org/c/boc/bocode/s336401.html> (accessed 2 December 2009).
 - Bradford LD (2002) CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. *Pharmacogenomics*, **3**, 229–243.
 - Evans WE, Relling MV, Rahman A *et al.* (1993) Genetic basis for a lower prevalence of deficient CYP2D6 oxidative drug metabolism phenotypes in Black Americans. *Journal of Clinical Investigation*, **91**, 2150–2154.