AACC Academy's Pain Management LMPG: Verification of Drug Dosing with Quantitative Urine Drug Testing?

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Clinical practice guidelines have become a mainstay for streamlining medical practices and function to ensure uniformity. Clinical practice guidelines are relevant in the world of laboratory medicine, given the large number of medical decisions that are based on the result of a clinical laboratory test. The first set of guidelines was created in 1995 by the National Academy of Clinical Biochemistry (now the AACC Academy) and was called "Standards of Laboratory Practice." The topic was the laboratory support of thyroid disease, and the guidelines were first published as a series of papers (*1*) and then widely distributed as a monograph. Later, guidelines were produced under the label "Laboratory Medicine Practice Guidelines" (LMPGs). In this issue of *JALM*, the Academy's latest LMPG addresses laboratory tests to monitor drug therapy in pain management patients (*2*). As an author of several other LMPGs, including one on laboratory tests to support cases of drug poisoning (*3*), a coauthor of a recently released toxicology guideline, the Clinical Laboratory Standards Institute Guideline on Toxicology and Drug Testing (*4*), and director of a pain management laboratory, I believe I am qualified to render an opinion.

The pain management executive summary is a document containing 40 recommendations broken down into several subsections. Space and energy (i.e., mine) do not allow me to comment on all. Therefore, I have taken the liberty to address a few of the recommendations that I believe are particularly important. Recommendation 19 states, in part, "… quantitative definitive urine testing should not be used to evaluate dosage of administered drug or adherence to prescribe dosage regimen." Recommendation 36 states "there is insufficient evidence to support the practice of normalizing quantitative results to creatinine or specific gravity or that doing so is an effective means of detecting compliance or misuse/diversion." Recommendation 40 states "there is insufficient evidence in the literature to determine if quantitative concentrations alone or in combination with a clinical algorithm improve the use of testing in terms of identifying compliance, efficacy, or noncompliance."

To obtain some marketing advantage, there are commercial pain management laboratories that perform exactly these non–evidence-based tasks: urine drug normalization with creatinine, individual data plotting onto a distribution of results from other patients taking these medications, and interpretation of results for the patient as being compliant, noncompliant, or toxic using a dosing algorithm. It is well known that the excretion of drugs into urine is highly dependent on several factors, including fluid intake, renal and hepatic

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function, presence of disease, metabolic rates, and coadministration of other drugs that are inhibitors or inducers of metabolism. Correction to creatinine excretion is inadequate given the high between-individual biological variation because of age, muscle mass, and dietary intake (*5*). Correction to specific gravity is even more problematic, as it is influenced by protein excretion, glucosuria, bacteria, dyes, and other factors (*6*).

In April 2015, 2 large pain management companies engaged in a contentious civil lawsuit surrounding the validity and infringement of a 2009 US patent (7585680) that was awarded to the Marshfield Clinic in Wisconsin. The patent's abstract stated, "The present invention provides methods for detecting and quantifying metabolites in a biological sample by measuring the concentration of a test metabolite in the sample and comparing that concentration against the concentration of the reference metabolite, enabling accurate metabolite concentration measurements to determine aberrant drug usage patterns" (*7*). Within the claims of the patent is the statement, "providing one biological sample obtained from a patient on a prescribed medication regimen, wherein the sample comprises at least one test metabolite, wherein in the sample is urine." The jury of the civil trial upheld the validity of the patent, i.e., stating that urine drug concentrations can be used to predict drug dosing, and awarded $8.6 million to the plaintiff (licensee of the patent) for infringement (*8*).

Although this patent was not specifically cited in the document, the Pain Management LMPG Committee has graded the strength of recommendation 19 as an "A," strongly recommends adoption (i.e., quantitative testing should *not* be used to evaluate dosage or adherence) and has graded the quality of the evidence of recommendations 36 and 40 as "I" and "III," respectively, insufficient evidence (to support normalizing quantitative results or use of an algorithm). I am left to wonder that if the Academy's LMPG document had been available during the trial, would the outcome have been different? Subsequently, the defendant was charged with fraud and racketeering (unrelated to this lawsuit) and has since filed for Chapter 11 bankruptcy. Irrespective of this court ruling, I concur with the LMPG documents in stating that drug concentrations in urine cannot be used to determine adherence to a dosage regimen. The 7585680 patent was based on the result of study involving methadone compliance that included a pilot study of 7 subjects and a confirmation group of 33 subjects (*9*). Based on these results, the authors concluded that measuring the urine methadone metabolite concentration when normalized to creatinine could be used to determine drug overuse or underuse in a clinical setting. No other pain management drugs were tested. Other than calculating the body surface area and lean body weight, there was no attempt to characterize the population tested, such as with pharmacogenetics or comedications.

Although the methodology of the approach of using urine to determine drug efficacy is misguided, there is nevertheless the need to determine therapeutic efficacy of patients on pain management beyond simple compliance. The LMBG's recommendation 6 states "the evidence does not support that alternative matrices (e.g., oral fluid, serum, hair) are more effective than urine drug testing for the detection of relevant over-the-counter medication, prescribed and nonprescribed drugs...." This recommendation may be true only because relevant clinical studies are lacking. I have every reason to believe that quantitative measurement of serum concentrations can be effective in determining efficacy and toxicity if therapeutic drug concentrations in serum for specific pain management medications can be established. The clinical laboratory has been performing therapeutic drug monitoring for many years for drugs with a narrow therapeutic index, such as anticonvulsants, antiarrhythmics, selected antibiotics, and immunosuppressants. Opiate and opioid

analgesics also have a narrow therapeutic index, thereby justifying therapeutic drug monitoring (*10*). Although the LMPG does not recommend use of pharmacogenomics testing to guide drug and dose selection, the document acknowledges the wide variability of metabolism rates to genetic variances in hepatic cytochrome P450 2D6, the enzyme most responsible for metabolism of pain management drugs. Interpreting drug efficacy in serum has more merit than using the normalization of urine drug concentrations. Although I do not advocate therapeutic drug monitoring for hair or oral fluids, perhaps this editorial could be used as a "call for research studies" in serum.

Returning to the pain management LMPG, although I have no doubt it will be of assistance to clinical laboratories, my hope is that the recommendations get into the hands of physicians who prescribe pain management medications and determine which laboratory to use (if not their own).

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REFERENCES

1. 1995 National Academy of Clinical Biochemistry Standards of Laboratory Practice Symposium on Thyroid Testing. Clin Chem 1996;42:119–92.
2. Jannetto PJ, Bratanow NC, Clarke WA, Hamill-Ruth RJ, Hammett-Stabler CA, Heustis M, et al. Executive summary of the American Association of Clinical Chemistry Laboratory Medicine Practice Guideline: using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med 2017;2:xx–xx.
3. Wu AHB, McKay C, Broussard L, Hoffman RS, Kwong TC, Moyer P, et al. The National Academy of Clinical Biochemistry Laboratory Medicine Guideline. Recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. Clin Chem 2003;49:357–79.
4. Kyle PB, Fuller DC, Garg U, Hammet-Stabler CA, Hoess E, Johnson-Davis K, et al. Toxicology and drug testing in the medical laboratory. 3rd Ed. Wayne (PA): Clinical and Laboratory Standards Institute; 2017:C52.
5. Reinhard M, Erlandsen EJ, Randers E. Biological variation of cystatin C and creatinine. Scand J Clin Lab Invest 2009; 69:831–6.
6. Burkhardt AE, Johnston KG, Waszak CE, Jackson CE, Shafer SR. A reagent strip for measuring the specific gravity of urine. Clin Chem 1981;28:2068–72.
7. Larson MEM, Richards TM. Method and device for monitoring medication usage. US patent 7 585 680.
8. Millennium must pay Ameritox $8.6M in patent row, jury says. https://www.law360.com/articles/646498/millennium-must-pay-ameritox-8-6m-in-patent-row-jury-says (Accessed October 2017).
9. Larson MEM, Richards TM. Quantification of a methadone metabolite (EDP) in urine: assessment of compliance. Clin Med Res 2009;7:134–41.
10. Overholser BR, Foster DR. Opioid pharmacokinetic drug–drug interactions. Am J Manag Care 2011;11: S276–87.