

# New edition of toxicology testing guide now out

January 2020—CAP Publications released this month the second edition of *Clinical Toxicology Testing—A Guide for Laboratory Professionals*, edited by Barbarajean Magnani, PhD, MD; Tai C. Kwong, PhD; Gwendolyn A. McMillin, PhD; and Alan H.B. Wu, PhD. The first edition was published in 2012.

*The book has 29 chapters divided into three sections: toxicology testing in the clinical setting, toxicokinetics and methodologies for the toxicology laboratory, and specific analytes (drugs and drug classes).*

*CAP TODAY spoke with Dr. Magnani about the new book. She is director of toxicology and chief of clinical pathology, Department of Pathology and Laboratory Medicine, Tufts Medical Center, and professor of anatomic and clinical pathology, and professor of medicine, Tufts University School of Medicine, Boston. Here is what she told us. (See excerpt below.)*

## **What can you tell us about the new chapters in this second edition?**

This exciting new edition brings updated and expanded chapters to reflect the ever-growing field of toxicology in a clinical laboratory setting. The new chapters are “Clinical Pathology Consultation for Pain Management Services,” which provides case study examples for the interpretation of toxicology results from patients on chronic opioid therapy; “Special Considerations in Pediatric Toxicology,” which provides practical and testing perspectives; “Method Validation in Toxicology Testing”; and “Novel Psychoactive Substances.”

## **Can you highlight for us a few of the updates (separate from the new chapters) that readers of the new edition can expect to see?**

Several individual chapters have expanded on previous work, including “Laboratory-Based Screening Assays in Support of Pain Management,” “Approaches to Broad-Spectrum Drug Testing in the Clinical Laboratory,” and “Alternate Specimens for Drugs-of-Abuse Testing: Oral Fluid.”

## **How does this book differ from other clinical toxicology testing books on the market?**

This book focuses not only on specific analytes but also on practice settings that pathologists and other lab medicine professionals encounter while supporting clinical toxicology testing. For those pathologists whose primary practice focus is not toxicology, this is a good go-to reference for how to provide toxicology services. Chapters on regulatory considerations, workplace drug testing, the hospital autopsy and toxicology, and pharmacogenomic testing are particularly useful. In addition, understanding newly emerging designer drugs, how to interpret drug testing results, and assessing different methodologies are also important considerations for a successful toxicology laboratory. Lastly, laboratories will find the templates for drug testing, frequently asked questions on clinical drugs of abuse testing, and information about CAP proficiency testing a unique resource.

## **In addition to you and your three co-editors, there are 20 contributing editors. What can you tell us about the contributors, and are some of them new to this edition?**

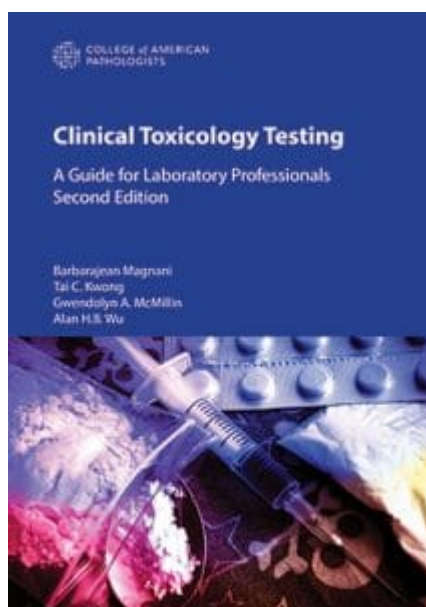
The CAP Toxicology Committee is a vital international resource to the clinical laboratory industry and has been fortunate to have as its members eminent scientific experts, many of whom have contributed to the writing of this book, as well as many equally renowned invited contributors who have authored many other books and peer-reviewed articles. The authors represent different toxicology perspectives and practices, including academic medical centers, nationally recognized reference laboratories, and forensic disciplines. This diversity of experience provides a well-rounded and useful guide for all who engage in toxicology testing.

## **What is the one biggest challenge for clinical toxicology laboratories today?**

The opioid crisis has placed considerable demands on the clinical laboratory, and laboratory professionals have been asked to partner with their clinical colleagues to help determine compliance with prescribed medications. Understanding the metabolism of specific drugs, the limitations of the various drug assays, and newly emerging designer drugs provides challenges for any toxicology laboratory.

To order (PUB227: \$80 for CAP members, \$100 for nonmembers), go to [www.cap.org](http://www.cap.org) (Shop tab) or call

800-323-4040 option 1. The ebook ( [ebooks.cap.org](http://ebooks.cap.org) ) is \$78. If you are interested in writing a book, contact Caryn Tursky at [ctursky@cap.org](mailto:ctursky@cap.org).



*Clinicians challenged with drug testing interpretation should be able to turn to laboratory professionals for guidance and clarification, and in some cases a clinical pathology consultation may be warranted. The most appropriate CPT code for that service is 80500 or 80502, say Dr. Magnani, Nicholas Heger, PhD, and Tai C. Kwong, PhD, in their chapter "Clinical Pathology Consultation for Pain Management Services." Here is the first of seven cases they include in their chapter (modified to protect patient health information).*

## Case 1

### Clinical Pathology Consultation

#### Comprehensive review of patient's history and medical records 80502; complex diagnostic problem

**Patient:** NAME and MRN

**Diagnosis:** Chronic pain: opioid-requiring (ICD10-F11.20)

The patient is a 70-year-old female with a history of hypertension, migraines, depression, degenerative joint disease, and chronic pancreatitis. The patient also complains of chronic pain and stiffness in her joints. In June she fractured her right foot and is currently wearing a boot. She currently takes Dilaudid (hydromorphone) and MS Contin (morphine) for pain. During a recent visit with her primary care doctor, a urine drug screen was performed and found to be presumptively positive for buprenorphine, methadone, THC-cannabinoids, and opiates. The patient's physician has requested a formal toxicology consultation in light of the unexpected positive buprenorphine and methadone results.

#### Past Medical History (per EMR)

Pain, hand  
Wrist drop  
Headache  
Chronic pain: opioid-requiring  
Chronic pain opioid: 2 week refill  
Hypertension  
Pancreatitis, chronic  
Dependence, continuous; MS Contin for chronic pancreatitis  
Degenerative joint disease, hands  
Pelvic pain  
Peripheral neuropathy  
Tobacco abuse  
Migraine, classical  
Depression

**Social History (per EMR)**

Tobacco: Current smoker, less than 1 pack per day.

Alcohol: Rarely.

Illicit drugs: Marijuana.

**Medication List**

Dilaudid 8 mg tabs (hydromorphone HCL) 1-4 tabs every 4 hours as needed for pain (max 8 day)

MS Contin 60 mg tabs (morphine sulfate) 1 tablet 3 times a day

Atenolol 50 mg tabs (atenolol) take 1 tablet by mouth daily

Norvasc 10 mg tabs (amlodipine besylate) take 1 tablet by mouth daily

Lyrica 150 mg caps (pregabalin) 1 tab twice a day

Evista 60 mg tabs (raloxifene HCL) take 1 tablet by mouth once daily

Cyclobenzaprine hcl 10 mg tabs (cyclobenzaprine HCL) once a day as needed for muscle spasms

Omeprazole 20 mg cpdr (omeprazole) take 1 capsule by mouth twice daily

Ranitidine hcl 150 mg tabs (ranitidine HCL) take 1 tablet at bedtime

**Laboratory data:**

### Urine toxicology screen (immunoassay)

Urine collected (DATE)	
Amphetamines	Not Detected
Barbiturates	Not Detected
Benzodiazepines	Not Detected
THC-Cannabinoids	DETECTED
Cocaine	Not Detected
Ethanol	Not Detected
Methadone	DETECTED
Opiates	DETECTED
Oxycodone	Not Detected
Buprenorphine	DETECTED

### Definitive urine toxicology lab results

#### Methadone quantitative, urine (LC-MS/MS)

(Laboratory where testing was performed)

Urine collected (DATE)	Limit of Detection: 100 ng/mL
Methadone	2500 ng/mL
EDDP (methadone metabolite)	12000 ng/mL

### Definitive urine toxicology lab results

#### Opiates expanded, urine (LC-MS/MS)

(Laboratory where testing was performed)

Urine collected (DATE)	Limit of Detection: 50 ng/mL
Codeine	Negative
Hydrocodone	Negative
Hydromorphone	1700 ng/mL
Morphine	>15000 ng/mL
Norhydrocodone	Negative
Noroxycodone	Negative
Oxycodone	Negative
Oxymorphone	Negative

### Definitive urine toxicology lab results

#### Heroin metabolite, urine (LC-MS/MS)

(Laboratory where testing was performed)

Urine collected (DATE)	Limit of Detection: 10 ng/mL
6-Acetylmorphine (heroin metabolite)	Negative

### Definitive toxicology lab results

#### Buprenorphine quantitative, urine (LC-MS/MS)

(Laboratory where testing was performed)

Urine collected (DATE)	Limit of Detection: 2 ng/mL
Buprenorphine	Negative
Norbuprenorphine	Negative

### Assessment:

#### Methadone

The urine immunoassay drug screen performed on the specimen collected on (DATE) tested presumptively positive for methadone. Definitive testing by LC-MS/MS (liquid chromatography-tandem mass spectrometry) identified both methadone (2500 ng/mL) and the primary metabolite EDDP (12000 ng/mL), confirming in vivo metabolism of methadone. Methadone is a synthetic opioid used to treat opioid abuse and withdrawal symptoms as well as for chronic pain. Methadone has a long half-life (15–55 hours) and is detectable in urine for several days after the final dose.

### **Opiates**

The in-house urine immunoassay drug screen performed on the specimen collected on (DATE) tested presumptively positive for opiates. This immunoassay is designed to cross-react with the naturally occurring opiates codeine and morphine, producing a positive result at concentrations of  $\geq 150$  ng/mL and  $\geq 300$  ng/mL, respectively. Definitive testing by LC-MS/MS identified morphine ( $>15000$  ng/mL) and hydromorphone (1700 ng/mL) only. No other common opiates/opioids were detected (ie, codeine, hydrocodone, norhydrocodone, oxycodone, oxymorphone, noroxycodone).

Morphine can be found in urine following administration of morphine itself (eg, MS Contin) or as the metabolite of either codeine or heroin. The concentration of morphine found in the urine ( $>15000$  ng/mL) is consistent with administration of morphine prior to the urine collection. Morphine has a half-life of 2 to 7 hours, and can be detected in the urine up to 2 to 3 days after the last dose. In light of the unexpected methadone immunoassay result and elevated morphine concentration, the urine sample collected on (DATE) was sent for definitive testing for heroin metabolites. The result of this analysis did not detect the heroin metabolite 6-acetylmorphine (6-AM). However, the absence of 6-AM does not rule out heroin use. Heroin, or diacetylmorphine, has an extremely short half-life (1-4 minutes) and is rapidly metabolized to 6-AM. 6-AM is also metabolized relatively quickly (3-52 minutes) to morphine.

Hydromorphone is a semisynthetic opioid (sold as Dilaudid) and is a major metabolite of hydrocodone (Vicodin) and a minor metabolite of morphine. Hydromorphone in the urine is consistent with administration of Dilaudid prior to the urine collection. However, given the concentration of hydromorphone was 1700 ng/mL, it is not possible to exclude that the hydromorphone is a metabolite of morphine. Hydromorphone has a plasma half-life of up to 9 hours and can be detected in urine 2 to 3 days after the last dose. Detection in the urine is dependent on both elimination patterns and the hydration status of the patient.

Note: Definitive testing did not include all well-characterized opiates/opioids (and as yet any newly emerging designer opioids) that may cross-react with the in-house opiates class immunoassay to produce a positive result. As such, it is not possible to exclude administration of other opiates/opioids not specifically tested for here.

### **Buprenorphine**

The in-house urine immunoassay drug screen performed on the specimen collected on (DATE) tested presumptively positive for buprenorphine. Definitive testing LC-MS/MS did not detect either buprenorphine or the primary metabolite norbuprenorphine. The buprenorphine immunoassay is not expected to cross-react with other individual opiates/opioids taken by this patient at low concentrations (ie, hydromorphone, methadone, morphine). However, when taken in combination, or at high concentrations (such as morphine or codeine), these opiates may be sufficient to produce a positive buprenorphine result. These findings suggest that the positive buprenorphine immunoassay result is a false positive. Buprenorphine is a semisynthetic opioid sold under the trade names Subutex (buprenorphine), Suboxone (buprenorphine and naloxone combination) and Butrans (transdermal patch), marketed for the treatment of opioid addiction. Due to its powerful analgesic and euphoric effects, buprenorphine may be abused or substituted for heroin or other opioids.

### **THC-Cannabinoids**

The in-house urine immunoassay drug screen performed on the specimen collected on (DATE) tested presumptively positive for THC-cannabinoids. Definitive testing was not performed. The in-house immunoassay detects metabolites of delta-9-tetra-hydrocannabinol (THC), the primary psychoactive component of marijuana. The patient's urine may be positive for 2 to 7 days after use or for up to 1 month in chronic smokers.

## Conclusion

In conclusion, the patient's toxicology results are not consistent with the prescribed medications. The positive immunoassay methadone result, as confirmed by LC-MS/MS, indicates administration of methadone prior to the urine collection. Definitive testing for opiates identified morphine and hydromorphone, consistent with the patient's prescriptions for MS Contin and Dilaudid, respectively, although one cannot exclude the possibility of hydromorphone as a morphine metabolite.

Definitive testing for buprenorphine was negative, indicating that the urine immunoassay buprenorphine result was a false positive, most likely attributable to cross-reactivity of the combined effect of the other opioids present in the urine. Definitive testing for THC-cannabinoids was not performed. Further investigation into the patient's possible use of unprescribed drugs should be explored.

Pathologist's Name: \_\_\_\_\_, MD

Department of Pathology and Laboratory Medicine

DATE and TIME STAMP

## Pearls

- With urine drug immunoassays, it is important to be familiar with cross-reactivity of both related and unrelated drugs, keeping in mind that a positive result may be attributable to the presence of one (or more than one) drug in the sample. An up-to-date and complete medication list of both prescribed and unprescribed drugs is essential.
- The absence of 6-AM in definitive testing does not exclude the possibility of heroin use. As heroin is metabolized rapidly to 6-AM and then relatively quickly to morphine, the absence of 6-AM may be a consequence of the time interval between last heroin use and urine collection. Similarly, the presence of morphine is not indicative of heroin use, as it may be the result of use of morphine-containing drugs, or as the metabolite of codeine, or consumption of contaminated poppy seeds. Avoid insinuation and overinterpretation regarding possible heroin use whenever 6-AM is not detected with definitive testing. Specific immunoassays for 6-AM are available.
- High concentrations of morphine (and codeine) can cross-react with buprenorphine immunoassays and produce a positive result.