“Practical Guide” to Urine Drug Screening Clarified

To the Editor: Moeller et al recently provided a timely and important review of urine drug screening. Drug abuse is a serious medical and social problem in the United States. Urine drug testing (UDT) to detect abuse and diversion of prescription controlled medications, as well as abuse of illicit substances, is increasingly important in clinical medicine. Physicians’ ability to accurately interpret UDT results, however, is poor. Education is critical; equally critical is the dissemination of accurate information. We would like to address several inaccuracies in the review.

Opioids. The authors correctly assert that fentanyl and oxycodone are undetectable by most urine screens for opiate drugs, but the reasons they provide are incorrect. Fentanyl is undetectable not because it has no metabolites (it does), but because the chemical structures of fentanyl and its metabolites differ radically from those of opiates (ie, morphine and codeine). Oxycodone is generally undetectable not because it is derived from thebaine—indeed, thebaine is a precursor to both codeine and morphine in the opium poppy—but chiefly because of a minor structural difference from opiates: a 14-hydroxyl group that prevents it from cross-reacting with opiate antibodies in screening assays. The authors state that semisynthetic derivatives of morphine are not used therapeutically because of their abuse potential. In fact, hydrocodone, oxycodone, and hydromorphone, all of which are listed in Table 4 as semisynthetic opiate derivatives, are among the most commonly prescribed opioids. The authors state, “Positive results for heroin abuse are caused by use of prescribed opiates, such as codeine and hydrocodone....” This is a misstatement. Codeine, morphine, (usually) hydrocodone, and heroin all yield positive opiate screens, but this means only that an individual has been exposed to an opiate. Exposure to heroin can be established only by demonstration of the 6-monooacetyl morphine metabolite by a specific confirmatory assay.6

Cannabinoids. The authors perpetuate outdated information that nonsteroidal anti-inflammatory drugs (NSAIDs) can produce false-positive results for cannabinoids on the Syva EMIT and other immunoassay systems. While this was once true (their reference is nearly 20 years old), Syva has solved this problem by altering the formulation of EMIT. This was never a problem for other immunoassays. The authors also state that hemp-containing foodstuffs can produce positive screens for cannabinoids. Again, while this was once true, a 2003 US Drug Enforcement Agency (DEA) ruling classified food and beverages containing any amount of tetrahydrocannabinol (THC) as Schedule I controlled substances, making it unlawful to manufacture, distribute, dispense, or import any such product without registration. This had an immediate effect on domestic manufacturers, whose hemp-containing products are now virtually free of THC.

Cocaine. Until several years ago, “Health Inca Tea,” a deconcanized product that indeed contained detectable quantities of cocaine, was commercially available in the United States. The importation of this and similar products has since been banned by the DEA. Whereas these products are available over the Internet, they are classified as Schedule II drugs, making illegal their importation and possession.

Amphetamine and Methamphetamine. Screening for amphetamine—a term that ordinarily refers to both amphetamine and methamphetamine—by immunochemical methods has always been problematic because the phenylethylamine drug class, with its various controlled and over-the-counter derivatives, provides minimal antigenic character. Table 3 lists methamphetamine among the causes of false-positive results, but in fact amphetamine immunoassays are intended to detect both amphetamine and methamphetamine. The l-enantiomer of methamphetamine, desoxyephedrine, is not a controlled drug and can produce a positive screening result, although most modern immunoassays have a considerable degree of stereoselectivity and are much less reactive with the l-enantiomer. The authors correctly note that gas chromatography–mass spectrometry (GC-MS), without modification to separate chiral compounds, cannot distinguish between controlled (and frequently abused) d-methamphetamine and its less pharmacologically active enantiomer, desoxyephedrine. However, specifications for workplace drug testing from the Substance Abuse and Mental Health Services Administration have established a standard for GC-MS confirmation of d-methamphetamine that requires the presence (at >200 ng/mL) of the metabolically demethylated product, amphetamine, since the l-enantiomer undergoes only minimal demethylation. Although there is a reference to this requirement in a footnote to Table 1, it is not explained in the discussion, leaving the impression that confirmatory testing by nonchiral GC-MS does not rule out desoxyephedrine use, when in fact it does if performed and interpreted properly.

Appropriate interpretation of positive and negative results from urine drug screens often requires consideration of many variables, a point that Moeller and colleagues’ review under scores. Misinformation, however, serves only to complicate the already difficult task that physicians face when using UDT as part of their clinical practice. We strongly urge clinicians to consult with a qualified professional (eg, certified Medical Review Officer or toxicologist) when questions arise about the meaning of results from UDT.

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In reply: We thank Drs Reisfield and Bertholf for their insightful comments regarding our recent article. While we appreciate their concerns regarding possible inaccuracies in our review, we would like to clarify some of these comments for the benefit of readers.

One of the first concerns they raise regarding opioids can be attributed to misinterpretation of connotation. We agree that fentanyl has metabolites, a concern when prescribing in clinical practices (eg, for elderly patients); however, our intended meaning was that fentanyl “lacks” the metabolites of morphine and codeine that are needed to elicit a positive response on a urine opioid screen. Along those same lines, we would like to clarify our passage regarding semisynthetic derivatives of morphine not being used therapeutically because of abuse potential. Actually, we were referring to illicit agents (eg, heroin), which are semisynthetic derivatives of morphine, not legal substances, such as hydrocodone or oxycodone. We agree that these latter agents are widely used and have substantial abuse potential. Last, we agree that exposure to heroin can be established only by demonstrating 6-monooacetyl morphine metabolites, and a paragraph in our review provided this information.

Drs Reisfield and Bertholf have also challenged our inclusion of an outdated reference regarding false-positive results from NSAIDS that can be observed using the Syva EMIT system. Indeed the Syva EMIT system was altered to fix the interference with NSAIDS in the urine cannabinoids test; however, our reference by Rollins et al used the revised assay by Syva and still produced 2 false-positive results with exposure to NSAIDS. We thought that this was a significant finding that should be reported. In addition, some hospital laboratories, especially in rural or impoverished communities, may still use the old Syva EMIT systems, and clinicians should be aware of this potential interference.

We, the authors, are well aware of the DEA’s stance that any amount of THC or cocaine in food and beverages is illegal. However, in view of the increased Internet sales of products and importation across borders (eg, from Mexico, Central America, and Canada) of herbal medicines, foods, and other products that could contain trace amounts of THC or cocaine, the use of these products cannot be ruled out in the United States. Our intended audience in this paper, practicing clinicians, should be aware of these potential interactions and inquire about herbal products with all of their patients.

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We agree with Drs Reisfield and Bertholf that amphetamine immunoassays are designed to detect both amphetamines and methamphetamine, as stated in the article. We would like to point out that the column headings for Table 3 should be “Potential agents causing positive results” instead of “false-positive results.” We recognize that this error could have contributed to misinterpretation of the table contents, and we apologize for this oversight.

We hope that our clarifications have allayed some of the concerns raised by Drs Reisfield and Bertholf. We recognize that the area of urine drug screenings is complex and often challenging for clinicians when dealing with unexpected results. This complexity prompted us to publish this review for the sole purpose of providing additional resources for clinicians in everyday practice. While this review is not intended to be the sole authoritative article on urine drug screening, we hope we have increased basic understanding of commonly abused agents and their effect on urine drug screens to aid in clinical decision making.