White Paper

Cross-reactivity in Immunoassays for Drug Monitoring: Know the Assay and Change the Conversation

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Introduction

Antibody-based immunoassay techniques have been the analytical tools of choice for drug monitoring through urine testing since their introduction in the 1970s by Syva Corporation of Palo Alto, California. Their simplicity and cost-effectiveness have replaced the more complex TLC (thin layer chromatography) and GC (gas chromatography) techniques over the past decades.

Supported by some and criticized by others, drug testing of biological specimens has played its role in the overall government and healthcare approaches to drug monitoring. The matter of drug use, misuse, or abuse is both ancient and contemporary. In the past couple of centuries, societies have witnessed a drug history, both impressive and distressing. The isolation of morphine revolutionized pain treatment in 1806, as well as the introduction of heroin (1898) and other semisynthetic opioids as morphine alternatives. Later, the introduction of synthetic opioids—starting with meperidine in 1939[1]—as well as the many waves of drug epidemic that followed, affected public health and society at large to extents never imagined.[2-4]

The development of immunoassays for drug testing was prompted by the implementation of mandated drug testing in the United States to ensure workplace safety in military (1971) and civil federal (1986) settings. In 1988, Mandatory Guidelines for Federal Workplace Drug Testing Programs were released to ensure the reliability of laboratory results in legal court proceedings (Federal Register/Vol. 52, No. 15, Monday, January 25, 1988). Such guidelines have been revised a couple of times since with changes to the testing panel and/or cutoff levels. Five commonly used drugs (classes, parent, or metabolites) were initially included:

- marijuana (cannabinoids)
- cocaine (benzoylecgonine)
- opiates (morphine and codeine)
- amphetamines (amphetamine, methamphetamine)
- phencyclidine

In 2010, MDMA/MDA (ecstasy) and heroin, were added to the testing panel (73 FR 71858 November 25, 2008), followed by oxycodone, oxymorphone, hydrocodone, and hydromorphone in 2017 (Federal Register / Vol. 82, No. 13 / Monday, January 23, 2017 / Notices) and fentanyl in 2025 (90 FR 4662 January 16, 2025).

In medical settings, immunoassays for drug testing have also been adopted to guide clinical practice, expanding from methadone clinics to programs for pain management[5,6] and substance-use disorders.

Today, immunoassays for drug screening are widely used in clinical or non-clinical settings, in-lab, or at point of care, as well as in various methodologies developed by companies such as Syva (EMIT), Microgenics and ThermoFisher Scientific (CEDIA), or Roche (KIMS), to name a few.

Why change the conversation

For as much as immunoassays are simple to perform and widely used, their intrinsic assay characteristics—notably cross-reactivities or lack of cross-reactivities—have made results interpretation rather complex. Such analytical properties, combined with other knowledge and/or factors (e.g., drug history, drug metabolism, or specimen characteristics), can result in both expected and unexpected results. More often, the latter are equated to false positive or false negative results, leading to overutilization or misutilization of these terms, both analytically and clinically, which undermines assay performance as a testing tool. Only a few publications have addressed the issue of inadequate use of the false-positive and false-negative terms, being "too narrow to encompass the larger universe of potentially misleading, inappropriate, and unexpected drug test results."[7]

Unexpected (aka false) immunoassay results have been described as limitations, issues, drawbacks, challenges, pitfalls, defects, weaknesses, or missed opportunities that negatively affect patient care or clinicians.[8-10] However, could such results also be a source of information that guides rather than misleads or confuses urine drug-result interpretation?

We believe it is time to change the conversation and refer to the immunoassay results as expected or unexpected, recognizing that unexpected results may have valid reasons, including—but not limited to—the intrinsic analytical properties of an immunoassay. If well understood, this could guide case resolution and not affect patient care.

Drugs: structural similarities and cross-reactivities in immunoassays

Why drugs are related

Drugs belong to the "small-molecule" family, with molecular weights mostly between 200 and 500 Da (Dalton). Therefore, as antigens, they have limited specific epitopes. Structural similarities or analogs are common within drug groups, notably the opiate, benzodiazepine, and amphetamine families. When immunoassays are developed, a target molecule is chosen to raise antibodies (polyclonal or monoclonal) that will recognize specific molecular features of the target. Because of structural or conformational similarities, antibodies can also recognize and bind to other molecules, depending on the extent of similarities. Such antibody interaction with similar, but non-target drugs, will trigger a positive response in the assay. This characteristic is referred to as cross-reactivity. Cross-reactivity is a measure of assay specificity, which can be broader or narrower, depending on the target molecule and the antibody generated.

How drug structures influence assay performance

The manufacturer performs cross-reactivity studies with both structurally similar and less similar drugs to establish equivalent cross-reactive concentrations at the cutoff of the target molecule and publishes the information in the product monograph. The degree of similarity is most often reflected in the extent of cross-reactivity—the stronger the cross-reactivity, the closer the equivalent cross-reactive concentration is to the cutoff level of the target molecule and vice versa (Table 1).

Table 1. Manufacturer-determined cross-reactivities in the EMIT opiate assay with morphine as the target molecule. Equivalent cross-reactive concentrations are shown for compounds structurally related to morphine. Synthetic opioids, such as methadone, fentanyl, and tramadol, are structurally different and unlikely to cross-react in this assay at typical concentration in urine specimens.

Compounds structurally related to morphine	Equivalent concentration (ng/mL) at 300 ng/mL morphine cutoff
Codeine	102–306
Hydrocodone	247
Dihydrocodeine	291
Hydromorphone	335
6-Acetyl Morphine (6-AM)	435
Levorphanol	480
Morphine 3-Glucuronide	626
Oxycodone	1491

Not all immunoassays show multiple cross-reactivities. The EMIT immunoassay for the cocaine metabolite benzoylecgonine is very specific to this target molecule (cutoffs 150 ng/mL or 300 ng/mL) with equivalent cross-reactive concentrations for cocaine or other metabolites (norcocaine, ecgonine, methyl ester, or cocaethylene) in the much higher ranges of µg/mL. Similarly, the EMIT immunoassay for methadone is highly specific for the parent drug, and therefore, antibodies do not recognize its metabolite EDDP; other cross-reactivities are only remote.

Manufacturer-established cross-reactivities, or lack thereof, are intrinsic analytical properties of drug immunoassays. They are not analytical errors; they are rather expected assay performance outcomes.

Cross-reactivities in immunoassays: changing the conversation

Expected or unexpected results?

Understanding the extent of cross-reactivities in each drug immunoassay—stronger or weaker, anticipated or not—is fundamental to the interpretation of its results, both analytically and clinically. Analytically, an immunoassay result is reported as either positive or negative against a set assay cutoff. Although such results are regarded as screens, preliminary results that may require confirmation—each screen result, positive or negative—will have an explanation according to assay specifications or other analytical, pharmacological, or specimen considerations. For healthcare prescribers, results may be expected or unexpected—the term "false" attributed to unexpected results should be used with caution when interpreting results for patient care. A single result may have more than one analytical or clinical explanation. Such distinction is not well understood by healthcare professionals using the test in their clinical practice, leading to misconceptions or misinterpretations of drug immunoassays.

Unexpected positive or negative screens: truly false or likely results?

Before labeling a result as clinically false, all reasons that could *likely* generate such result should be considered and the impact on patient care assessed accordingly. For instance, positive urine opiates screens can be due to several scenarios: from poppy seeds consumption to over-the-counter low-dose codeine-containing medication, to prescribed morphine use vs illicit use of morphine or heroin. All such results are analytically true positives. Drug history and self-reporting, combined with other clinical observations, should be considered to clinically validate a positive opiate result accordingly.

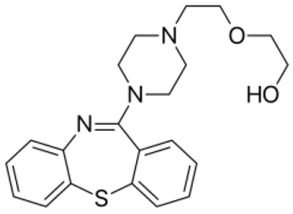
The EMIT urine benzodiazepines screen and other vendor benzodiazepines immunoassays have been conventionally developed to target diazepam use. Structurally related benzodiazepines, such as oxazepam and temazepam (which are also diazepam metabolites), strongly cross-react in the benzo assay and will trigger positive results when present. Some triazolo-benzodiazepines, notably alprazolam, cross-react strongly in the conventional benzodiazepine immunoassay. Positive screens due to alprazolam use are therefore not false positives, but rather likely expected results.

Understanding the lack of cross-reactivities, or how drug metabolism may affect known cross-reactivities, is just as important in the context of negative results. The case of benzodiazepines immunoassays best exemplifies this matter. Clonazepam and lorazepam show strong equivalent cross-reactivity as parent drugs in the EMIT assay at > 201 and > 600 ng/mL, respectively. However, they are quickly metabolized to 7-amino clonazepam and lorazepam glucuronide, respectively. The metabolites have very weak cross-reactivity, determined to cross-react at concentrations > 5300 ng/mL and 20,000 ng/mL, respectively. Not typically achieved with standard treatment protocols. For example, one study found 7-amino clonazepam levels ranging from 41 ng/mL to 6,000 ng/mL in patients in a standard pain program, with mean and median concentrations of 892 and 538 ng/mL, respectively; most frequently, levels were between 501-2000 ng/mL.[11] Consequently, negative results with the EMIT urine benzodiazepines screen assay when looking for compliance with clonazepam or lorazepam intake are not false negative, but rather likely expected results. Patients should not be at risk of being dismissed from a pain program due to physician misinterpretation of the likely negative results for clonazepam or lorazepam by immunoassay. Rather, a more appropriate assay (e.g., mass spectrometry), should be used to confirm clonazepam or lorazepam intake. Physicians can only rely on the results of the right assay for the questions they have.

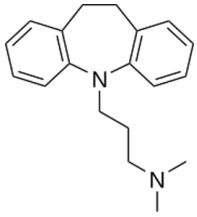
It should be recognized that the test name "benzodiazepines" can be misleading, as it might set false expectations for the users that it universally detects all benzodiazepines or metabolites in this very large family. This is not the case. Not detecting etizolam, a thienodiazepine in the triazolo class with the conventional benzodiazepines immunoassay should not necessarily mean false negative," rather a *likely expected result*.

Unexpected positive screens: not likely but still informative?

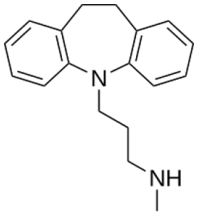
Some compounds are structurally related but have different pharmacological properties. Quetiapine is an atypical antipsychotic with a tricyclic structure similar to the conventional Tricyclic Antidepressants (TCA) (Figure 1) and was shown to cross-react in some immunoassays for TCA with both therapeutic use and in overdose.[12] Although such screening (preliminary) results are regarded as false positives by most users, some have found this cross-reactivity as reliable in screening for quetiapine adherence.[13]



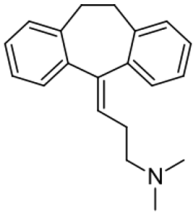
Quetiapine



Imipramine



Desipramine



Amitriptyline

Figure 1. Quetiapine has a similar three-ring structure with imipramine, desipramine, and amitriptyline, leading to cross-reactivities in TCA immunoassays.

Unexpected negative screens: false or invalid results?

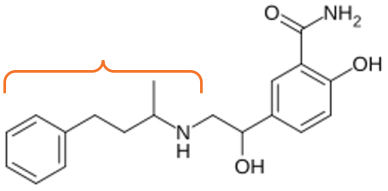
Very diluted urine specimens can lead to negative results in immunoassays. Analytically they are true negatives since dilution may affect the drug level below the assay cutoff. Clinically, these are invalid negative results rather than false negatives. The reason for urine dilution should be investigated (in vivo, in vitro) and additional urine specimen collection(s) should be requested to obtain valid results. At the same time, keep in mind that urine dilution may not affect the positive results, depending on the drug level prior to dilution.

Unexpected negative screens: false negatives or simply not tested for?

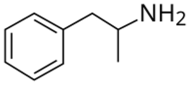
Equally important is to recognize that the number of drugs that can be screened for by immunoassays is limited by the commercial availability of an assay, in comparison with the number of drugs that can be identified by confirmatory laboratory-developed tests using mass spectrometry techniques. Drugs not typically included in immunoassay screens should not be compared with those detected in confirmatory testing and regarded as false negatives.[14] They are simply not tested.

Unexpected positive screens: false positives with the least informative value

Some cross-reactivities may be less expected and less informative and are more suitably regarded as true false positives as they have less informative value. The interference of quinolone antibiotics in opiate assays is such example.[15,16] Similarly—and less informative—are interferences caused by some drug metabolites detected in an unrelated immunoassay. For instance, labetalol metabolite APB (3-amino-1-phenylbutane) has been found to cross-react with antibodies in amphetamine immunoassays due to its structural resemblance with amphetamine. Labetalol is a preferred medication for managing hypertension in pregnancy.



Labetalol



Amphetamine

Figure 2. Labetalol metabolite ABP (3-amino-1-phenylbutane) has a similar structure to amphetamine, leading to cross-reactivity in amphetamine immunoassays.

There are other frequently reported interferences that can be considered true false positive screening results. For example, bupropion (a phenethylamine) can lead to a false-positive amphetamine result, and sertraline can lead to a false-positive benzodiazepine result.

Immunoassay cross-reactivities in the opioid drug epidemic

Limitations or information?

The matter of "false positive" or "false negative" results surfaced again as negative features in the new era of the drug epidemic. Introduction of illicit and diverse new psychoactive substances (NPS) lead to the interpretation that the immunoassays are becoming less effective, due to an increased occurrence of "false negative" and "false positive" results.[17]

One could think the contrary—cross-reactivities with structurally related substances have proven beneficial and informative in this new era of NPS availability, allowing new or unexpected information about patients' drug-taking behaviors. Immunoassay cross-reactivities not previously recognized led to the identification of designer benzodiazepines in urine specimens, notably flualprazolam and flubromazolam[17], as well as other drug analogs.[18,19] More recent in-vitro studies with drug-free spiked urine specimens demonstrated the ability of two commonly employed automated urine screening immunoassays, the ARK Fentanyl II and the Immunalysis SEFRIA fentanyl immunoassays, to detect an impressive number of more than 50 fentanyl analogs with modifications to the amide group or aniline ring of the molecule.[20]

The value of immunoassays should be recognized for what they are. Analytically, some are group specific, some are single drug (or metabolite)-specific, but both have their clinical values. It is not about poor sensitivity of established immunoassays for newer drugs, rather, about the need to develop new assays or improve current assays. The cross-reactivity of most drug glucuronides is poor in most immunoassays, but some assays have been improved by the addition of glucuronidase to increase the level of the parent drug.[21]

Immunoassay result interpretation

Know the assay…

Interpretation of immunoassay drug screening is a complex task. Assay specifications for sensitivity and cross-reactivities (specificity) must be well understood by the healthcare providers. Results should only be interpreted in the overall medical context of signs and symptoms, prescribed and non-prescribed medication, or suspected drugs.

There are many publications reviewing the immunoassay cross-reactivities.[22-23] However, while their interpretation is valid analytically, there is little-to-no emphasis on their overall potential for guiding rather than misguiding the course of action for patient care. They are mostly presented as sources of errors leading to legal ramifications, disrupting the therapeutic process of intoxicated patients, and leading the healthcare personnel to make incorrect diagnoses and decisions.

…and change the conversation

We need to change the conversation and focus on the education of healthcare professionals to be more knowledgeable of assay performance and less prone to assumptions or misinterpretations and see information rather than limitations in immunoassay results.

1. **Patient care should not be affected by the lack of knowledge** about the specificity of the assay that healthcare professionals are using. Mistakenly identified as issues with the testing methodologies.[24]
2. **Cross-reactivities, or lack thereof, are intrinsic attributes of immunoassays and should be regarded as informative rather than a limitation**. It is not about likely results causing confusion and affecting patient outcome,[25] but rather about knowing the assay specifications and working with them in the clinical context.

3. **Patient care decisions should not be based on assumptions**. For instance, synthetic opioids such as fentanyl or tramadol should not be tested for with the opiates immunoassay. The likely negative results for fentanyl or tramadol in such assays should not lead to the wrong assumption that patients are not taking the drug or diverting it.[26]
4. **Choosing the right assay for the right question is key to patient care**. The opiates immunoassay is universally included in drug-screen panels, but it may not be the assay of choice for oxycodone testing. However, knowledge about oxycodone cross-reactivity in the opiates immunoassay is important. This semi-synthetic opioid shares core structural similarity with codeine and morphine and shows variable equivalent cross-reactive concentrations in various vendor assay formats.[27] In the EMIT opiates immunoassay, the oxycodone concentration is 1,491 at the 300 ng/mL morphine cutoff. Such levels can be found in patients who take oxycodone for chronic pain immediately after the last dose, but they are more common in patients abusing oxycodone.[28]
5. **When in doubt, confirm**. *Guilty or not guilty?* This is not the question.[23] Rather, has the result been reconciled with the clinical picture or confirmed when in doubt? In the process of confirmatory testing, new and impactful cross-reactivities—not previously studied—may be identified. For example, loperamide, an anti-diarrheal mu opioid receptor agonist, can trigger positive results in certain first-generation fentanyl immunoassays when used in super-therapeutic doses.[29]
6. **There may be value in unexpected positive screens** even with a limited history of an unknown ingestion in a patient with an altered mental status, as often is the case in pediatric populations. Positive TCA screens have led to the diagnosis of carbamazepine intoxication.[30,31] *Knowledge of substances commonly cross-reacting on a given immunoassay screen can still lead the clinician to the correct diagnosis when interpreted with the clinical syndrome*.
7. **Newly identified cross-reactivities, not previously studied by the manufacturer, may be immunoassay format specific** (EMIT, CEDIA, KIMS, etc.) and should not be generalized to immunoassay technology.[15]

An important gap in the healthcare systems is that the laboratory professionals may not be sufficiently involved in the results-interpretation process. Their proficiency in immunoassay results interpretation may be overshadowed by the direct involvement of other health professionals, such as physicians, nurses, pharmacists—often with insufficient training.[32-34] Whenever in doubt and to avoid making an erroneous assessment that could harm the patient, trained laboratory professionals should be consulted to provide expert assistance with immunoassay result interpretation and case resolution.[35,36] They have access to and understand the manufacturer-determined cross-reactivities and are directly involved with quality assurance processes.

More efforts are needed to emphasize the informative value of cross-reactivities in medical practice and to provide healthcare professionals with the education they need to harvest the most of what is considered a harmful assay limitation.

Manufacturers should also participate in the larger effort to produce educational materials for their products by working closely with their laboratory customers. Product monographs should be periodically reviewed and cross-reactivities updated to reflect the ongoing dynamic of new prescriptions or new street drugs. Information in peer-reviewed publications on newly found cross-reactivities and their impact on patient care should also be considered for investigation.[27,37]

Conclusions

Immunoassays for drug monitoring are key analytical tools in various clinical and non-clinical settings. To use them with the least harmful impact on patient care, there is a need to understand what factors could contribute to unexpected results to accurately identify the course of clinical action. Inaccurate characterization of an immunoassay performance creates unnecessary confusion with unwanted impact and thus undermines assay utility. Not all cross-reactivities are equal, and they should be addressed in their own category for the best patient care decisions.

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