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ADLM Guidance Document on

Laboratory Testing for Drugs of Misuse to Support the Emergency Department

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TABLE OF CONTENTS

Toxicology testing for drugs associated with scenarios such as recreational use or substance use disorder can be performed in support of the emergency department (ED) for specific patient populations such as pediatrics and trauma. These compounds were historically referred to as drugs of abuse (DOA); although the word "abuse" is recognized as potentially stigmatizing, no replacement terminology for DOA has emerged in current guidelines. This document refers to these compounds as drugs or substances of misuse, and acknowledges the need for less-stigmatizing language that more fully encompasses the range of uses for these drugs. This literature-driven, consensus guidance document provides recommendations primarily targeted to US hospital-based laboratories performing urine drug testing (UDT) in support of the ED. Indications for ordering UDT and related testing in both pediatric and adult populations are summarized. Further, recommendations are made for testing that should be available at all facilities with rapid turnaround, and how to perform and report testing. The advantages and disadvantages of immunoassays and mass spectrometry, as well as common challenges, are reviewed. Indications for mass-spectrometry assays and more extensive testing (e.g., novel psychoactive substances) are also provided. Future directions for improvements in laboratory technology to improve the utility of this testing are outlined. All laboratories should collaborate with ED leadership, medical toxicologists and poison control centers to optimize and update test menus to reflect local drug use patterns, ensure test methodologies and results meet clinical needs, and educate clinical staff regarding assay limitations and accurate test interpretation.

INTRODUCTION

Toxicology testing in the emergency department (ED) is generally performed to detect either drugs with recreational or misuse potential, or a broad array of toxic or poisonous compounds. This document will address the former category of compounds, which have historically been termed "drugs of abuse" (DOA). Although the word "abuse" can imply a stigma, and is not a comprehensive term given the range of intended uses for these compounds, DOA is a well-known historical term and description. Although resources exist for language related to individuals who use these compounds (1, 2), there is no single preferred term to describe nonmedical use of these drugs. Replacing DOA with terms such as "recreational," "controlled," "illicit," or "non-prescribed" drugs was discussed, but none of these terms fully captures the range of clinically relevant scenarios involving use of these compounds. This document will refer to "drugs of misuse" as a parallel to the historical DOA terminology, acknowledging that future efforts should prioritize development of less-stigmatizing language that more accurately reflects the range of uses for these compounds.

Usage patterns of these drugs are highly situation-dependent and change rapidly; those most concerning for overdose, fatality, and other emergency presentations are discussed here. For historical and current trends, readers are referred to several excellent, curated online resources (3–8). Further, the measurement of blood alcohol and its clinical utility in the ED are not discussed in this document; toxic alcohols including ethanol will be discussed in the forthcoming Association for Diagnostics & Laboratory Medicine (ADLM) guidance document "Laboratory Support for Targeted and Comprehensive Toxicology Testing for the Emergency Department."

This document is not a systematic review but does reflect examination of the available literature (see Supplemental methodology) as well as expert opinion. The primary focus of this document is UDT as it is the most commonly tested matrix, but other specimen types will be discussed where appropriate. Relevant methodologies include automated or point-of-care (POC) immunoassays, considered "presumptive" or

Table 1. Toxidromes associated with exposure to substances of misuse.

TOXIDROME	SIGNS AND SYMPTOMS[a]	EXAMPLE DRUGS
Opioid	Miosis (pinpoint pupils), hypopnea/bradypnea, obtundation, hypotension, bradycardia, hypothermia, reduced peristalsis, lethargy, sedation, coma, delayed respiratory depression in pediatrics (especially young children)	Fentanyl and fentanyl analogs, heroin, oxycodone, other opioids (methadone, buprenorphine)
Sedative-Hypnotic	Lethargy, obtundation, bradypnea/hypopnea, hypothermia, stupor (in pediatrics), paradoxical excitation	Benzodiazepines, barbiturates, γ-hydroxybutyrate, gabapentin, pregabalin, zolpidem
Sympathomimetic	Tachycardia, tachypnea, hypertension, mydriasis (dilated pupils), diaphoresis (sweating), agitation/paranoia, seizures, hyperthermia, increased peristalsis, pediatrics: irritability, inconsolability	Cocaine, amphetamines, cathinones (bupropion)
Serotonin syndrome	Diarrhea, mydriasis (dilated pupils), fever, diaphoresis (sweating), agitation, tachycardia, clonus, flushing, hyperreflexia	MDMA, other substituted amphetamines, hallucinogens
Anticholinergic	Hyperthermia, tachycardia, mydriasis (dilated pupils), delirium, agitation/paranoia, seizures, dry/flushed skin, dry mouth, reduced peristalsis, thirst, urinary retention	Diphenhydramine
Cholinergic	Diarrhea, diaphoresis, urination, miosis (pinpoint pupils), bradycardia, bronchorrhea, bronchospasm, emesis, lacrimation, salivation, seizures, increased peristalsis Nicotinic: mydriasis, tachycardia, weakness, hypertension, hyperglycemia, fasciculations	Muscarinic mushrooms, nicotine

[a]Presentations differ by patient and may be impacted by factors such as age (pediatrics), comorbidities, and ingestion of other drugs or medications.

nondefinitive testing, and mass spectrometry, generally coupled with gas or liquid chromatography, and considered definitive or confirmation testing (see Supplemental glossary). The intended audience for this document includes all laboratories that provide toxicology testing for EDs or support testing at the POC. The recommendations are most relevant to nonreference, US-based laboratories, e.g., hospital clinical laboratories that primarily utilize immunoassay testing. International practices supporting drug testing for the ED can vary considerably from the United States and are not addressed. This document also does not cover forensic, legal, or workplace drug testing, chain of custody procedures, or postmortem drug testing as these are not part of routine ED workflows for clinical testing. However, it should be acknowledged that clinical specimens from the ED may be used for purposes beyond the original intent. This document is a collaboration between the Academy and Science and Practice Core Committee of ADLM.

WHAT ARE INDICATIONS FOR ORDERING DRUG OF MISUSE TESTING FOR PATIENTS IN THE ED?

The primary indications for ordering drug of misuse testing in the ED are in pediatric patients, trauma victims, and in patients with psychiatric or behavioral health problems. For acutely ill patients, physical examination guides management, but in some circumstances drug testing even after treatment initiation can provide clinical benefit. Patients presenting to the ED often exhibit characteristic symptom patterns referred to as "toxidromes" (Table 1); some laboratories offer testing tailored to specific toxidromes, whereas many others provide drug test panels that span multiple toxidromes.

Drug testing can assist with clinical management of patients presenting with altered mental status, where the differential diagnosis may be broad, although this is controversial (9). It is important to realize that a positive UDT can occur hours to days after drug exposure; the detection window for most drugs in urine far exceeds the duration of their physiological or psychological effects. In addition, prescription or over-the-counter medications can cause false-positive results, which may prompt unnecessary responses such as involvement of child protective services. Therefore, test results should be considered carefully in context of drug elimination, clinical history, physical examination, and other diagnostic studies.

Ordering and interpreting drug testing can be affected by conscious and unconscious bias. Individuals who use drugs are often perceived adversely by society. Clinical studies have shown that healthcare providers, with implicit biases toward people who use drugs, can negatively affect medical services provided to those patients, and that patients can be blamed for their health condition (10–12). The opioid crisis in rural areas is exacerbated by limited access to drug treatment services, and physician bias can become another barrier to equitable healthcare in rural areas (13). Implicit bias also exists in risk-based drug screening in pregnant women, in which low-income women and women of color are disproportionately targeted for drug screening (14). Drug testing should ideally be based on protocol to minimize risk of bias affecting patient care.

Infants and Young Children

Drug exposure in pediatric patients can occur through various mechanisms, depending on age. Neonates are most often exposed during delivery, e.g., opioid-based epidurals, or through maternal intake during gestation. Neonates and infants can also ingest drugs via breast milk, or if given (intentionally or unintentionally) by an adult caregiver. Toddlers and young children generally ingest drugs accidentally while exploring their environment or, less commonly, if provided by an adult.

Given their size, infants and young children can be at risk of toxicity even with small doses of a drug. Evidence indicates that growing use of opioids and decriminalization of cannabis has resulted in more pediatric emergency visits for these and other substances (15, 16). A systematic review of cases from states with decriminalized cannabis demonstrated increased ED visits from unintentional cannabis exposure in children <12 years. The authors suggested that cannabis exposure should be considered in any child with sudden-onset lethargy or ataxia (17). Similarly, toxic pediatric exposures to opioids, particularly fentanyl, were associated with risk of intensive care admissions and death (15).

Symptoms of intoxication are not always clear in infants and young children, and patients might not be able to verbalize a toxic exposure. UDT is an option for identifying drug exposure, but there are substantial limitations to this approach in pediatrics. Collecting a urine sample can be challenging, particularly from infants and toddlers. The decision to obtain a sample should be based on the clinical scenario and the risks and benefits because catheterization, if needed, can be stressful and traumatic. In addition, the small amounts of drug necessary to cause toxicity can translate into low concentrations that can lead to false-negative results.

Results of drug testing may help the healthcare team and/or child protective services assess the child's safety and well-being. For example, young children should not have independent access to drugs such as cocaine and, therefore, the presence of such drugs in their urine could prompt concern for neglect and/or abuse and the need to notify appropriate authorities.

Adolescents

Older children and teenagers present different challenges from a toxicological standpoint compared to younger pediatric patients. Additionally, adolescents are more likely to deliberately use drugs or experiment with various drugs of convenience such as inhalants, cannabinoids, over-the-counter compounds, or prescription medications diverted from friends or family (18). The Toxicology Investigators Consortium (ToxIC) reports that adolescent ED presentations vary widely in terms of signs and symptoms, and often lack available exposure history or a clear toxidrome (18). For some drugs, toxic symptoms can differ in adolescents compared with other ages, such as paradoxical excitation in benzodiazepine toxicity (19).

Although the risk of adverse outcomes due to drug exposure is often higher in adolescents than in younger children, ToxIC studies also note that UDT is often of limited utility and caution providers against over-reliance on toxicology testing in adolescents. This is due to several factors, including the type of drugs ingested by adolescents (e.g., novel psychoactive substances, NPS) for which there are few assays with generally slow result turnaround, limited sensitivity and specificity of available rapid assays, and the lack of meaningful impact on acute patient management (20, 21).

Given the potential medical and legal repercussions of drug test results, clear utility for testing should be apparent before ordering UDT in adolescents (22). Some EDs have established objective criteria for when to screen adolescents for alcohol or drug use; in one study this led to significantly improved detection of both (23). Several studies suggest routine substance use screening for all pediatric trauma patients (24); this strategy has been used to successfully target children and adolescents with drug-avoidance education (25). Although such results might not affect emergency care, long-term patient impact is also a consideration, such as screening children and adolescents for cannabinoid exposure due to the risk of altered neurological development and conditions such as psychosis (26). Laboratories should work with ED leadership and medical toxicologists to define the goals and protocols for drug testing in adolescents, and educate clinical staff on the risks of both over- and under-use of testing in this population.

Adult Populations

As with pediatrics, ED drug testing in adults should be clinically actionable (27), although this often takes the form of affecting clinical services downstream rather changing emergency medical care. For example, exposure to certain drugs such as methamphetamine has been shown to affect clinical services downstream of the ED and might help predict the need for mechanical ventilation or surgery (28, 29). Some institutions utilize UDT results performed during ED encounters to engage behavioral medicine or enroll patients in substance use disorder counseling (30). However, there are several considerations with performing drug testing for adult patients in the ED. The prolonged detection window of most drugs in urine can lead to positive UDT results after clinical effects of a drug have resolved. In contrast, commonly available methodologies (immunoassays, discussed next) might fail to detect clinically relevant compounds due to poor cross-reactivity (31). Laboratories should educate ED staff and other relevant practices, e.g., behavioral health, regarding the capabilities and limitations of available testing.

Within the ED, using UDT to differentiate psychiatric illness from mental status changes related to substance use is common, although the utility of UDT for this purpose has been questioned. Studies have demonstrated that use of UDT is associated with longer ED length of stay (sometimes due to waiting for test results) and has minimal impact on increasing

diagnoses of substance use disorder beyond what patients self-report (32–35). The American College of Emergency Physicians acknowledges that ED providers should consider the influence of alcohol or drugs on patients, but advises against routine UDT in alert individuals or delaying patient evaluation or transfer to psychiatric services while awaiting results of drug testing (36). However, some states require drug testing prior to, or as a component of emergency commitment (e.g., "72-hour hold" initiated by emergency physicians for substance use disorder or involuntary psychiatric evaluation). Laboratories should have mechanisms to ensure test results can be efficiently relayed to receiving facilities as appropriate.

Trauma is another common indication for ordering UDT in adults. The American College of Surgeons supports screening all adult trauma patients for substance use, using a variety of approaches that can include UDT (37). Caution is required to avoid over-interpreting UDT results in the context of trauma; important caveats are that negative results might not rule out intoxication, whereas positive results do not necessarily indicate impairment at the time of the traumatic event.

Recommendations

- ED and laboratory staff should collaborate to ensure objective protocols and/or clear clinical rationale are in place for ordering drug testing in pediatric and adult patients, considering that drug test results infrequently affect acute patient management in the ED.
- Laboratories should educate ED and other specialty providers regarding the limitations of UDT, particularly false positives, false negatives, and the possibility that the presence of a drug may indicate past exposure but not necessarily have a current impact on patient behavior.
- Laboratories should evaluate which drug testing methods best support pediatric care.
- ED and laboratory staff should have procedures to ensure proper sample collection, preservation, and testing or referral for specific populations including infants.

WHAT DRUG TESTING SHOULD BE AVAILABLE TO ALL EDS, AND HOW SHOULD TESTING BE PERFORMED AND REPORTED?

Test Menus

Relevant drugs and drug classes for which testing should be available to the ED are listed in Table 2. These include commonly misused and clinically relevant compounds: opiates and opioids, including fentanyl and oxycodone, as well as benzodiazepines, amphetamine-type stimulants, and cocaine. Table 3 outlines other drugs that could be considered depending on local usage, specific populations such as pediatrics, or intent of testing (e.g., coordination with behavioral medicine). In contrast to the 2003 National Academy of Clinical Biochemistry guidelines (38), propoxyphene and tricyclic antidepressants are not recommended for inclusion in UDT (Table 3) due to decreasing clinical use (39). Toxic additives such as xylazine and levamisole are also not recommended for inclusion in UDT, as these compounds emerge regionally and change frequently, and often lack commercially available options for testing. Many other clinically relevant drugs can be encountered in the ED for which testing cannot feasibly be offered by many laboratories due to lack of specific immunoassays or resources for mass spectrometry-based testing; these include NPS, synthetic cannabinoid receptor agonists, hallucinogens, dissociatives, and therapeutic drugs with recreational or misuse potential (40).

Table 2. Assays strongly recommended for inclusion in ED drug testing.

Strongly recommended for all locations	Common clinical cutoffs (ng/mL)
Amphetamine class	300, 500, 1000
Benzodiazepine class	200, 300; less common: 100, 150
Cocaine (benzoylecgonine)	150, 300
Fentanyl	1, 2, 5; less common: 20
Opiate class	300[a]; less common: 100
Oxycodone	100, 300

[a]The 2000 ng/mL opiates cutoff is appropriate for workplace/forensic testing, not clinical.

Although historically drug screens have been institutionally defined panels of detectable drugs, laboratory information systems, automated immunoassays, and mass spectrometry-based tests now facilitate greater flexibility in ordering and testing. In the United States, there is regulatory and payer movement away from bundling tests, which raises the question of whether the practice of offering drug test panels remains appropriate. However, the overlap in clinical presentation between various classes of drugs, and the risk for multidrug use, suggest that drug test panels are still appropriate, particularly in the ED. Tailoring panels to specific toxidromes is not required, and could be misleading particularly with multidrug use. Further, repeat testing (e.g., to evaluate clearance) is generally not needed; performing drug testing once in the ED is sufficient for patient management.

Test menus should mirror local drug use patterns to the extent feasible. While it is impractical for most laboratories to incorporate emerging drugs (e.g., NPS) or toxic additives (e.g., xylazine) into UDT, it is expected that even small or resource-constrained laboratories should remove rarely used drugs (e.g., propoxyphene) and incorporate more appropriate assays as they become available. The College of American Pathologists proficiency testing data indicate that laboratories have been

Table 3. Additional recommendations for emergency department drug testing.	
Consider based on local needs, e.g., pediatrics, substance use disorder treatment	**Utility and notes**
6-acetylmorphine	Specific heroin metabolite; immunoassays use much lower cutoffs than opiate class assays.
Buprenorphine	Might be used in referral to behavioral medicine or rehabilitation using medication-assisted therapy; less frequently for toxicity. Assay-dependent false-positive rates.
Methadone/EDDP	Immunoassays target either methadone or its metabolite EDDP, with little/no cross-reactivity to the other compound.
Phencyclidine (PCP)	Recreational usage is region-specific; testing in low-prevalence areas will lead to high false-positive rates.
THC	Indicated for pediatrics; the utility of testing in adults is driven by clinical presentation.
Sedatives, e.g., barbiturates	Drug facilitated crime; low prevalence of nonprescribed use.
Creatinine	Evaluates specimen integrity; assay is not expensive and is routinely available in most laboratories, but has limited utility in ED setting.
Adulterant testing, e.g., oxidants	Low likelihood of adulteration in ED setting.
Toxic additives, e.g., xylazine	Prevalence changes rapidly; test results unlikely to change clinical management in ED.
Minimal clinical utility: do not test	**Rationale for removing from test menus**
Propoxyphene	Removed from the US market >10 years ago, minimal recreational usage.
Tricyclic antidepressants	Less frequently prescribed and at lower dosages compared to past decades. Assays prone to false positives.
EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.	

slow to update test menus to include opioids such as fentanyl and oxycodone that are not detected on opiate class assays (41), despite >20 years of a North American opioid epidemic and increasing overdoses and deaths associated with fentanyl or its analogs. All laboratories supporting an ED should strongly consider offering fentanyl testing. Indeed, some US states have enacted legislation requiring incorporation of fentanyl into ED drug screens; as drug use patterns change laboratories should be aware that similar legislation may emerge for other compounds.

The value of including assays for tetrahydrocannabinol (THC) and its metabolites in ED drug testing is currently debated. Challenges include evolving laws for drug scheduling, legalization or decriminalization of recreational use, and provisions for regulated medicinal use; increasing use of products containing other cannabinoids such as cannabidiol (CBD) or delta-8-THC; and in the United States, provisions of the 2018 Agricultural Improvement Act (Farm Bill) regarding hemp-derived compounds (42, 43). For example, a positive result for THC metabolites is possible in patients using CBD products due to the presence of THC in the preparation. Regardless of legality, cannabinoid testing provides limited clinically actionable information in the ED, except in specific populations such as pediatrics. A systematic review evaluating the United States, Canada, and other countries showed that most studies reported increased cannabinoid-related poisonings post-legalization, particularly in children (44). In addition, THC use is associated with other phenomena that can lead to ED visits, such as cannabinoid hyperemesis, psychosis, and trauma; however, providers should recognize that THC metabolites can be detected in urine long after last use. While some studies in regions with legal THC use have reported negative outcomes such as increased mortality (25) or need for mechanical ventilation after trauma (45), the findings are inconsistent. Legalization of marijuana may influence the decision of emergency physicians and other healthcare providers to test for THC as studies have shown increasing rates of positivity as legalization progressed (46, 47). Drug test results might also influence other healthcare utilization; a Canadian study reported fewer ED orders for imaging and laboratory testing, and increased use of observation units in THC screen-positive patients after cannabis legalization (48). The clinical laboratory should be aware of local and national regulations when designing panels, and offer flexibility with test menus to improve utilization, such as offering separate drug panels with and without THC, and/or having THC as a standalone orderable test.

Drug Testing Matrices

The preferred matrix for most US laboratories remains urine, due to the availability of commercial assays, comparatively higher

drug concentrations, and ease of collection. However, urine can be difficult to obtain in nonresponsive or anuric patients. Oral fluid (saliva) has some potential advantages over urine, for example allowing noninvasive, witnessed collections (49). Also, the shorter window of detection in oral fluid might help distinguish remote drug use from recent exposure (50). Despite these potential advantages, oral fluid is rarely used in US EDs. In addition, there are limitations to oral fluid testing currently, including a higher rate of false negative results compared to urine and fewer commercially available assays (51, 52).

Drug concentrations in blood or serum/plasma can occasionally correlate with specific symptoms, but factors such as variability in time to presentation and individual tolerance make measuring blood concentrations for drugs of misuse other than ethanol less useful clinically (53). One exception is in patients with renal failure who cannot produce urine, but there are relatively few laboratories that offer serum or plasma testing for these drugs. From epidemiological standpoints, blood testing can provide meaningful quantitation of drugs for later investigation of fatal and nonfatal overdoses (54), NPS, and tainted drugs (55). Specific test matrices for newborns such as meconium or umbilical cord can offer simpler collection and longer detection windows (56).

Reporting Results

Drug test results should be available within a clinically relevant window (27). For the ED, this window is short (40). Previous recommendations to provide results within 1–2 hours might be longer than preferable for ED providers (38, 57). Furthermore, this turnaround is likely only achievable when performing POC testing or automated immunoassays in a laboratory near the ED. Laboratories with sufficient resources for dedicated instruments and personnel may achieve rapid turnaround using broader mass spectrometry-based options, but relatively few laboratories have such capabilities. All laboratories should discuss turnaround expectations with ED leadership to determine a feasible yet clinically meaningful goal, generally under 1 hour. Interventions to shorten the major components of turnaround time (order to collect, collect to receipt in the laboratory and receipt to result) will differ for preanalytical and analytical phases, and require a multidisciplinary team to address. Laboratories should have a robust mechanism for tracking result turnaround components in real time.

Results reporting, whether qualitative or quantitative, must be appropriate for the test used; some key considerations for reporting are listed in Table 4. If >1 modality of drug testing is available within an institution (for example, both POC and laboratory-based immunoassay), results should clearly distinguish the test performed and cutoff. Immunoassays are prone to false positives; qualitative report phrasing should reflect this. Although there is no consensus on the best terminology, cautious phrasing such as "presumptive," "preliminary," or

Table 4. Key elements and considerations for drug test reporting.

Report element	Considerations
Drug/drug class name	• Clarity for end user, e.g., "methadone metabolite" rather than or in addition to "EDDP." • Accuracy, e.g., "opiates" rather than "opioids", to highlight that synthetic opioids are not detected by class assays.
Matrix tested	• Drugs can be detected in urine after their clinical effects have ceased. • Detection windows in other matrices are generally shorter than urine.
Test methodology	• Especially important to distinguish when >1 type of drug testing is available within an institution. • Minimize laboratory jargon where possible to ensure clarity for end user.
Limitations (immunoassay and POC tests)	• Variable cross-reactivity within each drug class. • Risk of false positives and false negatives
Limitations (mass-spectrometry tests)	• Targeted assays can only detect the compounds specified. • Although uncommon (generally limited to NPS), compounds of the same molecular weight can be mis-identified as another drug.
Results	• Cautious phrasing, e.g., "presumptive" or "unconfirmed" positive for immunoassay and POC tests. • Qualitative vs quantitative reporting for mass spectrometry.
Cutoff	• Drugs present below the cutoff are reported as negative. • Commonly used cutoffs are historically based and might not be optimal for clinical utility in the ED, e.g., for pediatric testing.
Interpretative guidance	• Typical detection windows in the matrix tested. • For mass spectrometry, identification of metabolites and parent drug(s), e.g., "hydromorphone may be present after use of hydromorphone or as a metabolite of hydrocodone." • Laboratory, ED, and medical toxicology contact(s) for assistance.

EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.

"unconfirmed" positive has been suggested as more accurately representing immunoassay performance than simply "positive." While this terminology might be clear to laboratorians familiar with assay limitations, providers or patients might not recognize the implications of "presumptive" results. Furthermore, while the same concerns exist for immunoassay false negatives, similar cautionary wording is rarely used when test results are negative (e.g., "presumptive negative"). "Detected/not detected" and "present/not present" are alternative options, though still potentially confusing to end users.

Assay cutoffs should be easily accessible to individuals interpreting UDT, preferably reported alongside the results or in a result comment. However, there is no consensus for optimal cutoffs for either screening or definitive drug testing. Immunoassay cutoffs are frequently driven by assay manufacturers, whereas mass-spectrometry cutoffs are chosen by the performing laboratory. Common UDT cutoffs used in the United States are listed in Table 2. Immunoassay cutoffs are largely historical rather than evidence-based, and are intended to minimize false positives. Thus, there are specific scenarios where these cutoffs can be too high for clinical utility. Delayed presentation to the ED is a scenario where clinically relevant drugs might be present at concentrations below common cutoffs. Mass spectrometry-based testing allows for lower cutoff concentrations and improves sensitivity, but at the risk of increased reporting of drug exposures that are not relevant to emergency management of the patient. It should be noted that neither immunoassays nor mass spectrometry-based tests are entirely equivalent between manufacturers and/or laboratories, which may affect interpretation of results arising from different platforms.

Infants and children can experience toxicity after even small doses of drugs, which might translate into low concentrations in urine. Furthermore, detection of some drugs (e.g., cocaine) at any concentration in infants or children is concerning. Some laboratories have implemented lower cutoffs for pediatric testing to address this. One institution increased detection of pediatric cannabinoid and cocaine exposure by setting their immunoassay cutoffs to 50% of the manufacturer's recommendations, then confirming presumptive positives by chromatography (58). However, lowering cutoffs risks increasing false-positive results. Laboratories that opt to employ lower immunoassay cutoffs for pediatric testing must ensure providers are aware of the increased likelihood of false positives, the fact that cutoffs differ between pediatric and adult populations, and the rationale for this decision. Ideally, improved sensitivity for pediatric drug screening should be achieved with superior test methodologies (e.g., mass spectrometry with rapid turnaround) rather than with modified immunoassays.

The question of whether to flag results is challenging, as either negative or positive results may be expected depending on patient medications, assay performance, and/or clinical presentation. There can be value in flagging positives as "abnormal" to alert providers to consider results in the clinical context. Interpretative comments should accompany the results to provide additional clarity. Comments could include the assay cutoff, potential for false-positive or -negative results, assay cross-reactivity, need for definitive testing and/or who to contact with questions. Results and comments may be available for patients to view in electronic medical record patient portals, which should be taken into consideration when designing comments in collaboration with the ED. In addition, laboratories should be aware of federal and state laws surrounding results reporting and patient privacy, particularly with adolescents.

Laboratories using mass-spectrometry testing for the ED should consider whether qualitative or quantitative reporting is more appropriate. Quantitative reporting (especially of parent drug and metabolites) has been suggested as potentially advantageous in settings such as pain management or substance use disorder treatment to determine the parent compound ingested or detect simulated compliance (i.e., adding drug directly into the urine sample). However, there is little evidence to suggest that drug concentrations are helpful to emergency care. Quantitative reporting might also be misleading (e.g., a large amount of drug in highly concentrated urine being misinterpreted as overdose). For the ED, qualitative reporting is likely sufficient; laboratories choosing to report quantitative results should consider whether creatinine normalization is appropriate. For negative results, reporting "<X" where X is the limit of quantitation might be misinterpreted to indicate presence of the drug at a lower concentration. Reporting "not detected", "negative", or some combination such as "not detected <X" could be preferable. Laboratories should clearly distinguish mass spectrometry-based results from immunoassay, using phrasing that minimizes laboratory jargon (e.g., "by mass spectrometry" rather than "by LC-QTOF-MS/MS"), and educate providers regarding the different limitations associated with mass spectrometry vs immunoassays.

Recommendations

- Drug test panels and protocols should be reviewed periodically and updated to reflect local drug use patterns. Drugs that are rarely used or with minimal clinical impact for the local patient population can be removed from test menus, and relevant drugs with available assays should be incorporated, particularly synthetic opioids such as fentanyl.
- Laboratories should provide UDT results to the ED within a mutually agreed-on window, generally <60 minutes, and testing should be clinically actionable for emergency treatment and/or follow-up care.
- A single urine specimen on ED arrival is generally sufficient for UDT. Repeat testing or alternative matrices are rarely necessary within the ED but can

sometimes provide meaningful information to later investigations.

- Immunoassays should be reported qualitatively using terminology that reflects their inherent limitations, e.g., "presumptive positive" or "unconfirmed positive" and accompanied by interpretative comments that include assay cutoffs. Mass spectrometry-based screens should be reported qualitatively (e.g., detected, present) in a manner to distinguish them from immunoassays.

WHAT ARE THE ADVANTAGES AND DISADVANTAGES OF IMMUNOASSAYS FOR ED DRUG SCREENING?

Immunoassays have been the mainstay of UDT for the last several decades (59–61). The main advantages of screening immunoassays are rapid turnaround time and the ability to perform testing on automated high throughput instrumentation. Clinical laboratories associated with an ED will commonly have instrumentation that can perform at least a basic set of drug screening immunoassays with short analytic time. Automated clinical chemistry platforms using homogeneous immunoassays allow for introduction of new tests and removal of obsolete tests when needed. POC screening assays will in general provide faster turnaround time and may be located within the ED (62, 63).

Limitations of Drug Screening Immunoassays

Multiple factors influence drug screening assay performance, including immunoassay format, type and specificity of antibodies, and instrumentation (59, 61). Antibody cross-reactivity indicates the degree to which compounds (e.g., drugs, metabolites, endogenous molecules) can produce a signal on the assay. Some immunoassays utilize monoclonal antibodies to achieve better specificity while others use polyclonal antibodies to capture multiple drugs and metabolites within a broader drug class. Manufacturers of screening immunoassays attempt to balance detecting clinically relevant targets of the assay while minimizing detection of "off-target" compounds (false positives).

Limitations of screening immunoassays include false negatives, false positives, and lack of comparability between different manufacturers and laboratories (39, 41, 64–66). For drugs with low prevalence in the patient population being tested, screening assays with poor analytical specificity will have low positive predictive value. These limitations are further complicated when a drug cross-reacts with more than one immunoassay (e.g., some POC devices include separate assays targeted to amphetamine and methamphetamine (64)) or a drug is positive by one immunoassay and triggers a false positive on another (e.g., high-concentration codeine triggers a positive opiate result and can cause a false positive in some buprenorphine immunoassays (67)), making result interpretation challenging.

Immunoassays for drug screening can be broadly classified into 2 categories: those narrowly targeted toward a single drug and/or its unique metabolites (e.g., oxycodone/oxymorphone) and those detecting a class of drugs with multiple clinically significant compounds (e.g., opiates) (68, 69). Narrow target screening assays tend to have fewer issues with false positives, because the assays are designed to detect just 1 or 2 compounds while having minimal cross-reactivity with other compounds (66, 68, 69). For example, the cocaine metabolite benzoylecgonine is structurally distinct from most other drugs or metabolites commonly found in patient specimens, leading to excellent assay specificity (68–70)

ED providers may be unaware of the limitations of drug screening assays. The laboratory should provide clear communication with the ED on assay cross-reactivity and acknowledge that names such as "benzodiazepine screen" can be misleading as they imply cross-reactivity with all drugs in those classes. Many newer drugs such as synthetic cannabinoid receptor agonists or "designer" benzodiazepines are not detectable on current immunoassays or POC devices; reliance on these assays without recognition of limited cross-reactivity to such compounds risks missing serious toxic exposures, especially in adolescents and users of vaping products.

False negatives for screening immunoassays occur when there is failure to detect drug(s) and/or drug metabolite(s) within the targeted class (61, 65). For example, nearly all opiates screening assays utilize morphine as the assay target/calibrator. Thus, in theory the detection of morphine should be similar across opiates assays. However, cross-reactivity for related compounds such as hydrocodone, hydromorphone, and oxycodone varies considerably across different opiate assays (41, 59, 69). Some assays can only detect high concentrations of these other opioids and therefore produce false negative results at clinically relevant concentrations.

Information supplied by the manufacturers in their package inserts about the analytical performance of their screening immunoassays can be confusing (72). Package inserts report data on cross-reactivity for drugs, drug metabolites, and endogenous compounds. However, there is wide variability in the number of compounds tested and how this data is presented. Cross-reactivity data may use various units of measurement (e.g., ng/mL or µg/mL) and may be expressed either as a percentage cross-reactivity compared to the assay target, or as the concentration of compound that produces the same signal as the cutoff concentration of the assay target. For an opiates assay, 400 ng/mL codeine might produce an equivalent signal to 300 ng/mL morphine. The manufacturer may state either that 400 ng/mL codeine is equivalent to 300 ng/mL morphine or that codeine has 75% cross-reactivity relative to morphine. The cross-reactivity of relevant related compounds such as cannabis derivatives (e.g., delta-8-THC, delta-10 THC, tetrahydrocannabinolic acid, cannabinol, cannabigerol) may or may not be listed in the package insert, leaving a laboratory to determine this information and the clinician to require

assistance with result interpretation. In addition to manufacturer information, published literature contains reports of cross-reactivity including using computational tools and electronic medical record data mining to identify additional cross-reactive compounds (64, 68–70, 72–74). The clinical laboratory can assist the ED by synthesizing information from package inserts and literature sources into clinically relevant summaries in laboratory handbooks or drug testing guides, and/or by adding interpretive comments within the test report.

Point-of-Care Testing

POC screening assays can provide a rapid turnaround time (62, 75). This may be especially advantageous if the clinical laboratory is remote from the ED. However, challenges with POC drug testing include subjectivity and interindividual variation for manually read results, and regulatory compliance for nonlaboratory staff (61, 76). Some devices have inverse read-outs such that positive results are indicated by disappearance of a band, which might lead to misinterpretation, particularly by inexperienced users. There are also opportunities for error during manual entry of results. However, some POC instruments allow automated result read-out and interfaced reporting to the medical record. POC assays can also have a different regulatory status (e.g., CLIA waived) compared to laboratory-performed assays, but there are numerous regulatory requirements even for waived testing, including proper test cartridge and reagent storage, and proper documentation of controls and results.

POC screening devices typically use immunoassay technology, thus results are considered presumptive and analytical issues are generally similar to those of laboratory-performed immunoassays. POC device cutoffs can differ from laboratory-performed immunoassays, e.g., POC fentanyl cutoffs of 10–20 ng/mL vs 1–2 ng/mL for automated immunoassays (77). POC screening assays may be formatted into preconfigured panels; consequently, the analytes on the panel may be out of date with drug use patterns, e.g., including propoxyphene or lacking relevant opioids (41). The clinical laboratory can assist in offering assays for drugs such as buprenorphine and fentanyl that might not be included on POC devices. The clinical laboratory should be aware of POC testing within the ED and, ideally, collaborate with the ED on finding options that best fit clinical needs.

Recommendations

- Immunoassay performance characteristics depend on whether the assay is designed to detect a drug or drug class. The laboratory should educate ED staff on the performance of each assay and include interpretative comments to reflect performance.
- Drug screening at the POC has the potential for more rapid results, but laboratory and ED staff must recognize the regulatory and technical challenges as well as the drugs that can be detected at POC.
- Laboratories should assist the ED in defining frequent sources of false positives (cross-reacting compounds) and false negatives (poorly detected compounds) for the specific assays in use.

WHAT ISSUES ARE SPECIFIC TO COMMONLY USED DRUG SCREENING ASSAYS?

Amphetamines and Amphetamine-Like Compounds

Amphetamines comprise a class of phenethylamines with varying degrees of sympathomimetic (i.e., stimulating the sympathetic nervous system) activity (78). Screening immunoassays for amphetamines and related compounds can be confusing in terms of nomenclature and assay specificity (41, 59, 72). Amphetamine-related immunoassays include those using antibodies directed at methamphetamine only, amphetamine and methamphetamine, and 3,4-methylendioxymethamphetamine (MDMA, "ecstasy"). Laboratories should consider assay cross-reactivity within the drug class when selecting an amphetamines screen. Some POC testing devices will have more than one amphetamine-related screening test (e.g., amphetamine and methamphetamine). Specificity has traditionally been a challenge for amphetamine-related assays as a variety of compounds such as cough/cold medications (e.g., pseudoephedrine), weight loss medications (e.g., phentermine), and street drugs (e.g., amphetamine-like NPS or "designer drugs") can contain compounds structurally related to amphetamine or methamphetamine (38, 69). Prescribed medications, such as the antidepressant bupropion or a metabolite of the antihypertensive agent labetalol, can also cross-react (78–81). Prescribed medications such as selegiline are also metabolized to amphetamine. Conversely, many providers assume the attention medication methylphenidate cross-reacts in amphetamines immunoassays, when it generally does not (78). Package inserts for amphetamine-related screens often do not contain information on drug metabolites or NPS (72). Table 5 summarizes cross-reactivity of amphetamine and other drug screening assays.

Benzodiazepines

Benzodiazepines are a class of drugs with both therapeutic and nonmedical applications. Given the structural variety of clinically important benzodiazepines, marketed benzodiazepine immunoassays typically utilize polyclonal antibodies or multiple monoclonal antibodies to achieve broader specificity (72, 78). Benzodiazepine immunoassays from different manufacturers have variable false-positive rates. False positives can occur with compounds such as the antidepressant sertraline or the antiviral efavirenz (66, 69, 82). In clinical practice, false negatives can be a significant issue, especially for the widely prescribed benzodiazepines alprazolam, clonazepam, and lorazepam, or novel benzodiazepines that have emerged in recent years. Historically, benzodiazepine screening tests targeted diazepam or the closely related nordiazepam, oxazepam, or temazepam

Table 5. Cross-reactivities of common immunoassays.

Immunoassay screen	In-class compounds detected well by screening assays	Examples of documented false positives (not comprehensive)[a]	Comments
Amphetamine/ methamphetamine	Amphetamine, methamphetamine	Bupropion, labetalol metabolite, phentermine, pseudoephedrine, trazodone metabolite	• Variety of assays on market, some with broad specificity (including detection of MDMA) and others with more targeted specificity to methamphetamine • Variable cross-reactivity to designer amphetamine-like drugs
MDMA/Ecstasy	MDMA	Rare	• Generally high specificity • Some amphetamine or methamphetamine screening assays can also detect MDMA
Benzodiazepines	Diazepam, oxazepam, chlordiazepoxide, nordiazepam, temazepam	Efavirenz, oxaprozin	• Variable cross-reactivity for alprazolam, clonazepam, lorazepam (often improved for vendors who have updated assays) • Low/no cross-reactivity for nonbenzodiazepine sedative hypnotics such as zolpidem and gabapentin • Limited data on detection of designer benzodiazepines
Buprenorphine	Buprenorphine, norbuprenorphine	Morphine or codeine (some assays), loperamide	• Cannot distinguish simulated compliance from actual use
Cocaine	Benzoylecgonine (major cocaine metabolite)	Rare	• Generally high specificity
Opiates	Morphine, codeine, hydrocodone, 6-acetylmorphine	Quinolone antibiotics	• Variable cross-reactivity with oxycodone and hydromorphone • Often no cross-reactivity with synthetic opioids (buprenorphine, fentanyl, methadone)
Fentanyl	Fentanyl, norfentanyl	Labetalol metabolites	• Sensitivity is challenging due to low concentrations present in urine • Poor metabolite cross-reactivity in some assays • Variable detection of fentanyl analogs
Oxycodone	Oxycodone, oxymorphone	Rare	• No cross-reactivity with natural opiates

[a]There are numerous examples of compounds producing false positives on immunoassay drug screens, especially given the large number of marketed assays. Some of the most documented examples of false positives are included in this column. The laboratory and/or manufacturer-supplied test information (i.e., package insert) should be consulted if a false-positive or -negative result is suspected.

(69). Conjugated benzodiazepine metabolites such as lorazepam glucuronide often cross-react poorly in these assays. Some laboratories have incorporated glucuronidase pretreatment to account for this; similarly, some manufacturers have reformulated their benzodiazepine screens to achieve broader specificity for alprazolam, clonazepam, and lorazepam (72, 83). Further, most benzodiazepine immunoassays do not cross-react with nonbenzodiazepine sedative hypnotics such as zolpidem, gabapentin, and pregabalin. Clinicians should be aware of the extent of false-negative results with benzodiazepine immunoassays.

Cocaine

Cocaine is an alkaloid found in the coca plant (Erythroxylon coca). Cocaine has limited medical uses as a topical anesthetic, but is most commonly encountered as a recreational drug (78). Immunoassays designed to detect cocaine commonly target benzoylecgonine, one of the main metabolites. As mentioned before, immunoassays for cocaine tend to have high specificity given the structural uniqueness of benzoylecgonine relative to other clinically relevant drugs (68–70). Benzoylecgonine may be detected up to several days after recent use. Positive cutoffs of 150 and 300 ng/mL for benzoylecgonine are common in immunoassays marketed for detected of cocaine. In the ED setting,

detection of cocaine may be consistent with a stimulant-related toxidrome or other presentations such as rhabdomyolysis (84).

Opiates and Synthetic Opioids

Opioids are a group of compounds with analgesic properties due to their ability to bind opioid receptors.

Opiates are naturally occurring (e.g., morphine and codeine), while synthetic opioids (e.g., buprenorphine, hydrocodone, oxycodone, fentanyl, methadone) are not (78). In clinical practice, many healthcare professionals use the terms "opiates" and "opioids" interchangeably. Opiates screening immunoassays commonly use free (unconjugated) morphine as the assay target and calibrator. Clinical cutoffs are typically 100 or 300 ng/mL; the workplace testing cutoff 2000 ng/mL should not be used clinically (41, 59, 78). Opiates immunoassays have varying degrees of cross-reactivity to opioids that are close in structure to morphine, including codeine, 6-acetylmorphine (heroin metabolite), hydrocodone, hydromorphone, oxycodone, and their conjugated metabolites. In clinical practice, this can lead to variable detection of opioids by opiates assays. The laboratory can assist the ED in providing information on opiates assay cross-reactivity and its clinical implications. Opiates immunoassays tend to have minimal cross-reactivity with buprenorphine and oxycodone, and essentially no cross-reactivity with opioids such as fentanyl and methadone. False positives with opiates screening assays tend to be uncommon, although some assays show cross-reactivity with quinolone antibiotics (66, 74). Consumption of large amounts of poppy seeds can lead to positive results at clinical cutoffs.

Oxycodone is an opioid that metabolizes to oxymorphone. Oxymorphone was marketed as a drug in the United States starting in 2006; extended release oxymorphone was subsequently removed from the US market in 2017 but immediate release formulations are available. Most opiates assays have essentially no cross-reactivity to oxycodone, oxymorphone, and their metabolites within the urine concentrations encountered in the clinical population (41, 69). This led to the emergence of specific immunoassays for oxycodone/oxymorphone. Given the prevalence of oxycodone use and the specificity of oxycodone immunoassays, they should be included in the UDT panel along with opiate immunoassays (39).

Fentanyl is used clinically as a rapid acting analgesic and sedative, as well as in chronic pain management. Fentanyl emerged as a major recreational drug by the late 2000s and early 2010s. Widespread availability of illicit fentanyl and, more recently, fentanyl analogs has contributed to a substantial public health crisis, particularly as these compounds are present in many unregulated drugs often without the consumer's knowledge. Screening immunoassays for opiates have essentially no cross-reactivity for fentanyl (41, 78). This has led to development of specific fentanyl immunoassays, although even by the early 2020s fentanyl immunoassays were available for some major chemistry instrumentation only as third-party assays. A study of proficiency testing for immunoassays revealed that adoption of fentanyl immunoassays was slow relative to the rise in public health concerns related to fentanyl use (41). The high potency of fentanyl leads to low concentrations in urine and other biological fluids, challenging the sensitivity achievable through immunoassays. False-positive results in patients taking labetalol, particularly pregnant patients, have been reported (85). Further, fentanyl immunoassays have variable cross-reactivity with fentanyl analogs. Many fentanyl immunoassays have poor cross-reactivity with the primary metabolite, norfentanyl, although some newer assays have partial cross-reactivity or target norfentanyl itself (86, 87).

Specific immunoassays for other synthetic opioids such as buprenorphine and methadone are available (88). Availability of immunoassays for other synthetic opioids is influenced by the type of instrumentation within the clinical laboratory, as these assays may only be available as open channels from third-party vendors on certain instrument platforms. Detection of buprenorphine and methadone may have limited value for the adult ED, but might help support substance use disorder treatment and other aspects of behavioral health. However, for pediatrics, the detection of buprenorphine can alert the clinician to the need for longer observation times and to alert local poison control for guidance. Children can experience life threatening and delayed respiratory depression from buprenorphine (89).

Recommendations

- Laboratories should attempt to optimize detection of relevant compounds such as glucuronidated benzodiazepines and synthetic opioids.
- Laboratories should communicate test-specific cross-reactivities and limitations (e.g., false positives) to their ED providers.
- Laboratory, ED, medical toxicology, and poison control staff should collaborate to determine the optimal test menu for their patient population, e.g., whether to include specific assays for synthetic opioids.

WHAT IS THE ROLE OF MASS SPECTROMETRY-BASED TESTING TO SUPPORT THE ED?

ED and laboratory staff should be aware of compounds missed by immunoassay screens in UDT panels and options that exist for testing these if needed. Many laboratories supporting EDs are resource constrained and are often limited in their ability to offer more sophisticated drug testing. Due to this, smaller hospital laboratories may send mass spectrometry-based testing to a reference laboratory or only offer testing for certain, more limited, drug classes. However, when used judiciously, mass spectrometry-based testing can be an effective tool to support the care of patients presenting to the ED, without adding unnecessary cost or complicated workflows (40). Confirmatory

or definitive tests using mass-spectrometry methods are more sensitive and specific than immunoassays, and can be helpful in specific scenarios, although they are rarely available in time to directly influence emergency care.

Despite the comparatively slow turnaround of results, mass spectrometry-based testing offers several advantages over rapid POC or laboratory-based immunoassays (90–92). Most importantly, mass spectrometry can provide identification of specific drug(s) or metabolite(s) present in the sample. Mass-spectrometry testing can also be useful when the provider suspects exposure to atypical drugs or drugs that are not detected by immunoassay, especially in patients whose history is unavailable or unreliable. Given the comparatively poor sensitivity and specificity of immunoassays, manufacturers typically suggest confirmatory testing for presumptive positive results, so care teams can rule in or rule out exposure to a specific drug. The utility of confirmatory testing may be higher for immunoassays with extensive cross-reactivity profiles and substantial false-positive rates (e.g., amphetamines), rather than relatively specific immunoassays (e.g., benzoylecgonine, a cocaine metabolite). Scenarios with legal or behavioral health implications, especially when involving pediatric patients, are additional indications for mass spectrometry-based testing (93). Although outside the scope of clinical testing for the ED, mass-spectrometry testing that covers many drugs in one analysis may also be useful for toxicovigilance or public health monitoring purposes, particularly due to frequent presence of multiple active compounds or toxic adulterants in unregulated recreational drugs (94, 95).

Most of the limitations associated with MS can be attributed to cost and assay complexity. Mass spectrometry requires specialized equipment and knowledgeable laboratory staff, both of which make these tests more expensive to develop and maintain for patient use. Mass-spectrometry testing also requires sample preparation, increasing the time and cost of analysis; the higher cost of mass spectrometry-based testing is likely transferred to the patient and/or their insurance. To better support laboratories performing this testing, CPT (Current Procedural Terminology) codes should be expanded to more accurately reflect newer drugs and technologies as well as to ensure adequate reimbursement (96). Further, mass-spectrometry testing is often sent to a reference laboratory or batched, leading to a longer turnaround time (typically days) compared to immunoassays (minutes to hours). Providers must consider when results will be available and if, despite the longer turnaround time, the results will impact patient management especially for patients who may be transferred or discharged by the time results are received.

Mass-spectrometry tests are most useful when they can detect drugs that are prevalent within the regional patient population. This requires laboratories to continually update their panels to reflect changes or trends in drug use and can introduce additional expenses. Most laboratories do not have the resources for more specialized toxicology testing including designer drugs or NPS that evolve rapidly. Therefore, it falls to specialized centers or reference laboratories to offer this testing, leading to longer turnaround times due to their distance from the patient bedside and shipping/transportation logistics. Specialized testing may be designed to detect drugs and drug classes that do not have known treatments, tests for compounds with atypical toxicity, or drugs for which rapid turnaround is not required because emergency treatment for the patient would not change with compound identification. These drugs, for which specialized mass-spectrometry testing may be needed, include: cathinones and pyrovalerone derivatives (e.g., bath salts), sedative hypnotics (e.g., designer benzodiazepines, ɣ-aminobutyric acid analogs), dissociatives (e.g., ketamine), psychedelics and synthetic hallucinogens (e.g., phenethylamines, psilocybin), synthetic cannabinoid receptor agonists (e.g., JWH-018), synthetic opioids (e.g., fentanyl analogs, nitazenes), stimulants (e.g., designer amphetamines), other NPS (e.g., kratom), and toxic additives (e.g., xylazine, levamisole).

Toxicosurveillance is an emerging public health tool to obtain data on the proliferation and use of designer drugs and NPS (97). The most common approach is to save specimens that have been ordered for clinical purposes from EDs or similar settings, and send them to public health laboratories for mass-spectrometry assays that can detect a wide array of substances (95, 97). However, toxicosurveillance should be conducted as part of a dedicated and funded program that complies with applicable laws (e.g., CDC Overdose Data to Action (98)), as this testing is outside the scope of clinical testing in the ED. Toxicosurveillance provides data on substances that may be missed by routine clinical toxicology testing, adding more detail to other data sources such as local or national poison control data (99). On a national scale, the most robust system for toxicosurveillance of designer drugs and NPS has been developed in Australia (100). Challenges for toxicosurveillance include securing funding for testing and data dissemination, as well as the logistics of retaining, identifying, and transporting potentially relevant samples to surveillance laboratories.

The identification of NPS and other designer drugs by analytical methods is limited by the frequency of structural changes to the compounds produced, which affects the ability to create standards/stocks for targeted analytical methods for these compounds. Additionally, knowledge of metabolites and appropriate detection targets is often lacking for NPS. Exposure to NPS may produce adverse effects that mimic symptoms of one or more of the toxidromes found in Table 1. However, if testing options are not available for drug identification, then the patient could receive treatment or supportive care to resolve the clinical symptoms. On the contrary, patients exposed to more than one compound may display mixed toxidrome symptoms, which complicates the treatment of care and identification of drug exposure. Testing for NPS can be beneficial for poison control

centers to track drug trends and to alert healthcare providers. The identification of unknown compounds could be performed using an untargeted drug screen approach using high-resolution mass spectrometry (101).

Toxicology testing using mass spectrometry is subject to several limitations, and currently considered high-complexity testing. Each laboratory performing mass-spectrometry testing for a given drug may have slightly different procedures and therefore results might not be comparable between laboratories. Similarly, the choice of which drug(s) and metabolite(s) to include in assays and the cutoffs used to report positive results on mass-spectrometry testing can also vary widely between laboratories. Some follow more conservative forensic guidelines for cutoffs, while others opt to report results that are closer to the analytical limits of detection. Interferences in mass-spectrometry assays include compounds that co-elute, or are isobaric or isometric to the analyte of interest; this is particularly a concern with NPS given the rapid evolution of structurally similar compounds. Future developments to improve the utility of mass spectrometry for ED support could include FDA-cleared devices, automated instruments, and remote data review capabilities; although they are not yet widely adopted, ambient ionization techniques may reduce the need for sample preparation and reduce turnaround time (40).

Recommendations

- Mass spectrometry-based tests are most useful when the patient's history is unreliable or unavailable, when the patient has a presumptive positive result for an immunoassay that has broad cross-reactivity, or when the drug in question cannot be detected by immunoassay. However, mass-spectrometry testing is not recommended, in any of these scenarios, unless the result could change patient management or inform follow-up care for the patient.
- Confirmatory tests provide less value when a rapid screening result is concordant with the patient's history or prior test results. This is particularly true for immunoassay screens that have high rates of confirmation (e.g., benzoylecgonine).
- Due to its superior sensitivity and specificity over immunoassays, mass-spectrometry testing should be considered for specific patients including pediatrics or when results could facilitate downstream patient care such as psychiatric support.
- ED staff should recognize that immunoassays and many confirmatory testing panels might not detect designer drugs or NPSs. If testing is required, the provider should work with the laboratory to identify and send out testing to a specialized toxicology laboratory.

HOW CAN THE CLINICAL LABORATORY SUPPORT THE ED BEYOND PERFORMING DRUG TESTING?

Test Interpretation

Evidence suggests that many clinical providers do not have sufficient training to correctly interpret urine drug test results (102–110). Most studies assessed the knowledge of non-ED providers, but one study did report that most emergency physicians were unable to name the drugs tested at their hospital (103). Another found that most ED providers reported little to no training in drug test interpretation, and accordingly demonstrated educational gaps particularly related to detection of opioids (107). Inaccurate interpretation of drug test results can have serious clinical consequences. Therefore, these studies recommend improving the knowledge of healthcare providers.

The clinical laboratory should be involved in creating educational materials related to drug testing and interpretation (91). One study demonstrated that an educational intervention improved residents' understanding of drug test results (111). Results reports can also be updated to assist with accurate interpretation (91). Educational comments may be attached to results, for example: "This screening test was performed using immunoassay technology which may produce false-positive or false-negative results. For questions or to request confirmatory testing contact the laboratory." In addition to a comment, laboratories may include links to educational information in a laboratory handbook or provide test-specific interpretative comments such as common causes of false negative or positive results.

Despite a lack of evidence within emergency medicine of the efficacy of laboratory medicine consultations or formal interpretations, studies in pain management suggest providers find such support valuable (112, 113). Similarly, it has been recommended that the laboratory have knowledgeable personnel who can be contacted if there are questions regarding drug test interpretation (91, 110, 114). Studies have also shown that the availability of experts in medical toxicology leads to the improved management of poisoned patients (115).

Ideally, sites offering drug testing should provide not only educational tools and resources but also experts in medical and laboratory toxicology, either internally or by partnering with other entities such as poison control. However, there are many challenges with education including frequent turnover of clinicians and trainees and maintaining expertise and educational resources. Alert or comment fatigue is also common and can limit the utility of these mechanisms to provide meaningful education and interpretative support.

Test Menus and Clinical Impact

Collaboration and frequent communication between ED clinicians and clinical laboratory professionals are critical to ensure appropriate utilization of toxicology testing (27). Due to resource constraints, technical expertise and space limitations,

most laboratories cannot provide a full spectrum of drug testing. Therefore, laboratorians need to meet with their ED and medical toxicology colleagues to design the test menu, specimen type(s), reporting structure (e.g., quantitative vs qualitative results), and desired turnaround time. For all testing scenarios the cost and clinical impact should be considered.

Order sets should be frequently reviewed and UDT tests or panels should be removed if not clinically indicated. Ongoing review of the test menu with the ED, at least yearly, is recommended as drug use patterns change and new testing becomes available. Positivity rates may help guide decision-making. For example, a site may decide to remove the phencyclidine (PCP) screen if positivity rates for PCP in their laboratory are low (41). Protocolized orders for drug testing in particular patient populations such as trauma and behavioral health patients should also be reviewed and adjusted as needed (116). It is important to understand the clinical utility of all drug tests. If resources permit, case reviews to document the clinical impact of drug testing will be informative.

Resources for evaluating drug patterns and test menus include the National Drug Early Warning System (117, 118) for emerging drug trends, and the National Institute on Drug Abuse Community Epidemiology Work Group Network (119), to identify illicit drug use, synthetic compounds, and other agents. The Substance Abuse Mental Health Services Administration and America's Poison Centers provide annual reports of drug exposure in the United States (120). International drug surveillance programs can also be utilized to identify NPS trends (121–126).

Specimen Storage

Clinical laboratories should have documented procedures for specimen collection, transport, and storage. Many laboratories are not accredited to perform forensic testing and therefore are not required to have chain of custody. Despite this, requests from the medical examiner's office or law enforcement to obtain specimens and/or perform recreational drug or NPS testing may occur. Therefore, it is recommended that laboratories consider saving negative specimens for 48 to 72 hours and all positive and pediatric specimens for a more extended period of time. Specimens, at a minimum, should be stored refrigerated. Risk management and legal teams at an institution support the clinical laboratories and should be consulted if needed.

Additional testing on archived specimens from the ED may also be helpful for the overall management of ED patients. Commonly, drug ingestions are not reported by patients or suspected by clinicians (127), and the earliest-collected specimen is generally the most likely to enable detection of drug exposure prior to arrival. Therefore, as discussed previously, enhanced or surveillance toxicology testing on deidentified specimens may be useful to better understand local drug use including novel drugs and adulterants as well as risk of overdose. These data can also allow public health agencies to identify and monitor trends.

Recommendations

- The clinical laboratory should provide resources and educational material to assist the ED with interpretation of drug test results. Laboratories should consider appending generic or specific comments to results that clarify test performance..
- Experts such as laboratorians, medical toxicologists and/or poison control staff should be available for consultation and assistance with test interpretation.
- The clinical laboratory should review the drug test menu, including protocolized orders, with the ED periodically. The test menu should reflect local drug use patterns and results should guide patient management.
- Chain of custody documentation is not required for clinical drug testing. However, the clinical laboratory should consider the feasibility of saving negative specimens for 48 to 72 hours and any pediatric specimens or specimens with 1 or more positive results for a longer period in case additional testing is required.

FUTURE DIRECTIONS

As noted throughout this document, there are numerous limitations to the utility of testing for drugs of misuse in the emergency setting. It is unrealistic to expect that FDA-approved immunoassays will be available quickly enough to support screening for NPS or other emerging compounds; mass spectrometry must be utilized. Unfortunately, the analytical performance of immunoassays is insufficient to provide clinically meaningful identification of even common drugs, without substantial risk for misleading or inaccurate results. Hospital laboratories need better tools to support the ED. Laboratorians and clinicians should advocate for changes that would improve the utility and accuracy of drug testing in the ED. Clinical scenarios for reflex algorithms (immunoassay screen followed by mass-spectrometry confirmation) or, preferably, direct to mass-spectrometry testing should be defined. Both these options require the development of mass-spectrometry testing that is available, affordable, accurate, user-friendly, adaptable and rapid. The reimbursement for mass-spectrometry testing should also be evaluated to ensure laboratories have sufficient funding to maintain a robust testing program.

Until mass-spectrometry technology improves sufficiently to support rapid testing for the ED, more robust tools to educate clinicians on immunoassay performance are needed as well as discussions with manufacturers on how they can assist with this education (e.g., making the name of the test more indicative of its cross-reactivity such as amphetamine/methamphetamine instead of amphetamines). Historically defined cutoffs should be evaluated for sensitivity and specificity, and optimized if needed to provide greater clinical utility. The advantages of other matrices

for drug testing, such as plasma/blood or oral fluid, should be explored to determine utility in the ED (e.g., distinguishing recent vs remote exposure); this will require increased development and availability of assays targeted to these matrices.

SUMMARY AND CONCLUSIONS

Drug testing within the ED provides minimal benefit for many patients, but can be valuable in pediatrics or specific scenarios with long-term clinical implications. Immunoassay and POC testing will likely remain the dominant methodologies in this realm for the foreseeable future. However, expanding availability and improvements in ease and rapidity of mass spectrometry have the promise to greatly increase the utility of drug testing in emergency medicine. Laboratorians and clinicians should advocate for these advances.

Regardless of the method(s) offered, all laboratories should collaborate with ED leadership, medical toxicologists and poison control centers to ensure test menus are up to date and reasonable for the patient population. Results reporting should acknowledge the limitations of presumptive methods and provide sufficient detail to accurate interpretation, including cutoffs and appropriate comments. Laboratories should ensure ED providers recognize which drugs can and cannot be detected, and facilitate access to expanded testing when clinically necessary. Laboratories and EDs should collaborate on education of clinical staff regarding assay performance and limitations and regularly discuss optimal strategies to meet clinical needs.

Supplemental Material

Supplemental material is available at The Journal of Applied Laboratory Medicine online.

Nonstandard Abbreviations

ED, emergency department; DOA, drugs of abuse; UDT, urine drug testing; POC, point of care; ToxIC, Toxicology Investigators Consortium; NPS, novel psychoactive substances; THC, tetrahydrocannabinol; CBD, cannabidiol; MDMA, 3,4-methylendioxymethamphetamine.

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The corresponding author takes full responsibility that all authors on this publication have met the following required criteria of eligibility for authorship: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved. Nobody who qualifies for authorship has been omitted from the list.

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