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Point-of-Care Urinary Drug Screening

By Hoi-Ying (Elsie) Yu, PhD, DABCC, FAACC

Introduction

Point-of-care (POC) urinary drug screening provides fast turnaround of results. Therefore, it can be an attractive test option to some providers. However, limitations of POC drug screen testing make it less than ideal in many situations. Most importantly, users must be aware of the limitations to prevent misinterpretation of results that could lead to false accusations of drug use or medication non-compliance. Here, we explore the limitations of POC urine drug testing, while also providing context on when they may be useful, and perspectives from practicing providers.

Why POC Testing?

In most case, POC testing is used because of the fast turnaround time and the need for immediate patient evaluation. Having the results right away allows the provider to give immediate consultation to the patient, which improves patient engagement. It also saves time by not having to track down patients after the last encounter (see Box 1, Interviews with providers at Geisinger Health System). In other situations, the results are critical for patient care. This is most apparent in my conversation with Dr. Margaret Jarvis (Division Chief, Addiction Medicine, Geisinger Health System). Many of the patients she encountered suffered from severe withdrawal symptoms. Toxicology results are needed to treat the patients from both clinical and regulatory standpoints. Per Pennsylvania state regulation, patients must be drug-dependent and currently using opioids to receive buprenorphine (and methadone) treatment. Therefore, a urine drug test showing positive opioids is needed for the patient to be eligible for treatment. Second, to prepare patients for buprenorphine treatment, the determination of recent fentanyl use is critical as buprenorphine treatment in those patients may precipitate withdrawal symptoms. Unfortunately, addiction clinics/hospitals do not always have a clinical laboratory on site, so the use of a POC drug screen test is helpful. Both Dr. Jarvis and Justin Troutman, PharmD (Clinical Pharmacist for Pain Management, Geisinger Health System) caution that providers must have a good understanding of the limitations of the POC drug tests to avoid misinterpretation. In their opinions, when toxicology results do not match clinical presentation, it provides an opportunity for discussion with the patients and sometimes the laboratory. Decisions should not be made solely based on test results. However, it is important to consider that the patient self-reported drug use may not be accurate either.

In other cases, the use of POC testing is due to its lower cost. Depending on the health insurance, the out-of-pocket cost cannot be ignored. However, the limitations of POC drug screens (see below) in combination with a general practitioners' lack of understanding of toxicology results (1, 2) can lead to misinterpretation of results and an increased risk of patient mismanagement.

How Do POC Drug Screens Compare with Drug Screens Performed by Laboratory-Based Immunoassays?

As with most laboratory-based drug screens, POC drug screens are primarily immunoassays and results are considered presumptive as there is a possibility of false positive and false negative results. Immunoassay methodologies detect classes of

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drugs based on "shape matching" of the epitope (drug of interest) and antibodies. Therefore, structural similarity could result in a false positive result. Conversely, false negatives often result from the low cross-reactivity of the drug of interest. For example, most opiate immunoassays primarily target codeine and morphine. Opioids such as oxycodone, hydrocodone, and fentanyl do not always have high cross reactivity with the opiate screen depending on the specific assay (3). Similarly, reactivity of each benzodiazepine to the screening method varies and is dependent on the assay. Not all commonly prescribed benzodiazepines can be detected by a benzodiazepines screen. For example, the assay that we use does not reliably detect lorazepam and temazepam usage (4).

From an accuracy perspective, most trained laboratory professionals consider the laboratory-based immunoassay drug screens more reliable. There are multiple reasons for this. First, the laboratory-based immunoassays are typically performed on more sophisticated automated instruments by trained laboratory professionals. Second, most laboratories perform test validation/verification prior to implementation, while many doctor offices and clinics use waived POC toxicology screen cups without any evaluation. The test verification/validation process identifies what tests are accurate or problematic (e.g., high rate of false positives or negatives) and determines other test limitations. Instead of implementing tests with known issues, alternative test reagents can be explored and implemented. Third, good laboratory practice typically has other ongoing quality assurance processes in place, which include daily quality control, proficiency testing, and patient result comparison with mass-spectrometry based confirmatory tests which provide information on test accuracy and specificity. Therefore, toxicology screens performed by a good quality core laboratory typically have fewer false positives and false negatives.

However, some POC urinary drug screen tests are probably sufficient for clinical use in certain settings. In our experience, performance of POC toxicology cups varies widely. We evaluated 6 commercial POC urine drug screen tests (5). While we considered 4 of the POC drug screen tests acceptable (overall concordance with mass-spectrometry results 89%–96%), the other 2 had either technical issues (e.g., urine fails to migrate in the test strip) or poor concordance with confirmatory mass-spectrometry results. It is therefore important to complete test evaluation to avoid selecting tests that have analytical issues.

Is Drug Screening Useful?

Although both POC and laboratory-based immunoassay drug screen results are not definitive, screening results are generally available within a reasonable time (same day if not within hours from order) compared to mass-spectrometry based confirmatory test results (usually several days from order). In addition, the preliminary drug screen results often yield enough insight for clinical evaluation in emergency settings. Therefore, it continues to be the main tool for identifying drug overdose cases in emergency room settings.

Not surprisingly, different service lines have different drugs of interest. Sometimes, the test nomenclature with numbers signifies the number of drug classes being screened (DAU7 means 7 drug classes are screened, DAU9 means 9 drug classes are screened). This nomenclature may imply more is better but this may not necessarily fit the clinical need. Over time, that has resulted in confusion as to which drug screen panel to use. At Geisinger Health System, we have standardized our drug screen panel to a single panel, which we update periodically as drugs of abuse trends change. For example, we have eliminated a barbiturates screen from our drug screen panel as it is no longer commonly abused and have added other specific opioids that are commonly abused such as hydrocodone and fentanyl. For our providers who need toxicology testing for pain medicine compliance monitoring, we created a specific panel to aid that process where medication information is provided upon order entry, and the laboratory in turn uses that information to ensure the drug of interest will be tested (e.g., if a patient is taking tramadol, a tramadol confirmation will be performed since it is not being screened).

Why Is POC Drug Cup Not Typically Sufficient?

Compared to laboratory-based drug tests, waived POC toxicology cups have a limited test menu. For example, there is no Clinical Laboratory Improvement Amendment (CLIA)-waived fentanyl screening test (6), even though fentanyl abuse has been on the rise in the US in recent years. On the other hand, many of the drug cups still screen for barbiturates, propoxyphene, or phencyclidine (PCP), even though these drugs are no longer commonly used. With the ever-changing trends in drugs of abuse, waived cups may not always meet testing needs.

As for pain management, a drug screen alone (whether POC or laboratory based) is not always sufficient. One issue is that the drug of interest may not be included in a screening test (e.g., tramadol). Another issue is that drug screens do not usually identify the specific drug. For example, if the opiate screen is positive, one is unable to determine which opioid(s) are causing the positive. This usually is not of concern for patient management in the emergency room setting. However, in pain management settings, there is a difference between knowing whether the sample only contains the parent drug, versus both parent drug and metabolite. The

determination of metabolite helps ensure that the patient has indeed taken the medication as opposed to dissolving a pill in urine to alter the results of the drug test. In addition, drug screen tests do not provide quantitative results. In the cases of "dissolving pill in urine," the concentration of the parent drug is unusually high. So, the quantitation aids in confirming such suspicion. However, it should be noted that urine drug concentrations should not be used to determine dosage information (7). It may only be helpful if the concentration is substantially higher than expected (e.g., 100–1000-fold higher than other patients in similar dosage). In those cases, the quantitation can be helpful.

Conclusion

Timely drug screen results are necessary in the management of patients in emergency settings, whether because of suspected overdose or drug dependency issues. However, in the day-to-day pain management and addiction treatment settings, 2–5 days for turnaround of accurate toxicology results is reasonable based on my conversations with Drs. Jarvis and Troutman. Faster results from POC testing may be attractive, but that is not to be overlooked by the limitations previously stated. General practitioners may lack experience in toxicology testing to understand the intricate differences between screening and confirmatory testing. Clinical laboratory support is needed to ensure good quality of testing.

Box 1, Interviews with providers at Geisinger Health System—Margaret Jarvis, MD, Division Chief, Addiction Medicine; Luke Sullivan, DO, Associate Director, Department of Emergency Medicine; Justin Troutman, PharmD, Clinical Pharmacist for Pain Management

In your opinion, would POC Toxicology Cups improve the clinical service you provide? Please explain why or why not.

JT (Pain Management): I believe POC testing can be both an improvement in toxicology services for primary care but also introduce potential for problems as well. POC testing is a valuable resource that provides real time feedback for a provider while the patient is within the office. This can increase quality of communication for patients and help strengthen the provider/patient relationship. I also believe that with POC testing must also come a degree of awareness on how to interpret these results, as they are not as clearly defined as confirmatory testing methods. There are high chances for false positives and false negatives with POC testing, which could lead to misleading assumptions from the provider who may not have proper training in interpreting results from this type of method.

LS (Emergency Medicine): No. We have a urine tox panel that we use now that is relatively quick to return. It is not a hindrance on our ability to diagnose or disposition patients.

How do you handle false positive or false negative results? Or when toxicology results are not matching clinical presentation?

MJ (Addiction Medicine): First thing—talk to patient! A lot of time, patients admit to drug use. When a patient is engaged with the treatment relationship, they are more likely to open up.

Decisions should never be made with just a data point (laboratory result only). However, not all providers understand the limitations of POC drug screen tests. Some patients are only being seen by social workers with not a lot of knowledge in drug testing. Providers with addiction fellowship training typically understand the limitation of POC testing, though.

JT (Pain Management): While most drug testing methods carry a level of scientific certainty, the clinician does often need to leave some room for nuance, especially if the suit does not fit. False positives and false negatives provide opportunity for further testing (if available) and further clinical discussion with the patient. A compromise can often be reached between 2 parties in these cases. While there is no definitive method on how to handle these situations, the clinician does need to take a lead role in starting the discussion on how to move forward when results are not what were expected. This could mean a re-test, increasing monitoring parameters for a certain window of time until the clinician feels more comfortable, or potentially changing therapies. Across the board, "take the patient's word for it" is not the best strategy, as patients engaging in aberrant behaviors or struggling with addiction tend to rely on this method to secure further supply of their drug of choice. At the very least, there is always a chance to have a conversation with the patient.

What are the limitations for the current toxicology testing services?

LS (Emergency Medicine): We can test for most common recreational and prescription drugs including benzodiazepines, opiates, methadone, amphetamines, and cannabinoids in our urine tox. Additionally, we frequently order ethanol, acetaminophen, and salicylate (all blood tests), as well as many psychiatric and anti-epileptic drugs (blood tests). Perhaps one limitation to our

current testing would be the inability to determine the timing of ingestion.

MJ (Addiction Medicine): Although the turnaround time for urine toxicology test is not bad, it is not always adequate to support the decision that needs to be made in the addiction hospital/clinic. In addition, most clinics do not have core laboratory on site and are in area that rely on courier services for laboratory testing. Other than that, the routine drug screen panel is okay. Addiction specialists have enough knowledge and know the test limitations. They would request specific tests as needed.

Learning Objectives

After reading this article, the reader will be able to describe pitfalls of point-of-care urine drug cups. The reader will be able to list situations where the use of point-of-care urine drug cups may be warranted.

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Special thanks to Margaret Jarvis, MD; Luke Sullivan, DO; Justin Troutman, PharmD for participating in an interview with me for this article. More importantly, I would like to thank them for working with the laboratory to ensure optimal test utilization for patient care.

Reference

1. Reisfield GM, Webb FJ, Bertholf RL, Sloan PA, Wilson GR. Family physicians' proficiency in urine drug test interpretation. J Opioid Manag 2007;3:333–7.
2. Reisfield GM, Bertholf R, Barkin RL, Webb F, Wilson G. Urine drug test interpretation: what do physicians know? J Opioid Manag 2007;3:80–6.
3. Opiates II Testing Reagent [Package Insert]. 2020-09. English. Indianapolis, IN: Roche Diagnostics; 2020.
4. Benzodiazepines Plus Testing Reagent [Package Insert]. 2016-08. English. Indianapolis, IN: Roche Diagnostics; 2016.
5. Sneidman M, Yu HYE. Performance comparison of six different rapid screening drug test cards/cups. Clin Chem 2015;61:S220 (B-319).
6. US Food and Drug Administration. CLIA–Clinical Laboratory Improvement Amendments–Currently Waived Analytes. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/analyteswaived.cfm?start_search=F (Accessed July 2021).
7. Nafziger AN, Bertino JS. Utility and application of urine drug testing in chronic pain management with opioids. Clin J Pain 2009;25:73–9.

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The Current State of mRNA Therapeutics and Their Associated Challenges

By Vrajesh Pandya, PhD

The central dogma of molecular biology includes messenger ribonucleic acid (mRNA) as an intermediate in the flow of genetic information from deoxyribonucleic acid (DNA) to proteins. Transcription of coding regions of DNA generates single-stranded mRNAs, which undergo splicing, maturation, and then transport across the nuclear membrane to be delivered in the cytoplasm. Ribosomes translate mRNAs to produce specific proteins, which serve various biological functions by acting as enzymes, immune-modulatory molecules, and structural components. The concept of using mRNA as therapeutics was conceived in the 1990s with the idea that temporary genetic information can be delivered in eukaryotic cells to produce specific proteins (1, 2). However, short mRNA half-life and limited means of delivery into tissues hampered progress in this area.

Recent advances in in vitro transcription (IVT), synthetic nucleotides, as well as cationic lipid-based delivery systems have led to the successful development and clinical trials of mRNA therapeutics for infectious disease vaccines (e.g., COVID-19), cancer immunotherapy (e.g., melanoma), and protein replacement therapies (e.g., methylmalonic acidemia) (1-4). Additionally, other ribonucleic acid-based therapeutics including Patisiran, Fomivirsen, and Pegaptanib have been developed and approved by the Food and Drug Administration (FDA) for the treatment of hereditary transthyretin-mediated amyloidosis, cytomegalovirus retinitis, and age-related macular degeneration (4). The advantages of using mRNA as opposed to DNA include immediate translation in the cytoplasm, no need to deliver molecules into the nucleus, and averted risk of genomic insertions possible with DNA (2). mRNA therapeutics are also easier and faster to produce, unlike protein-based biopharmaceuticals, which require recombinant DNA expression and protein production in microbial fermentation or cell culture systems followed by elaborate protein purification steps (2). However, the regulatory practices for mRNA therapeutics are not yet clearly defined and the long-term effects of this class of drugs are not yet well-

understood (2). In the following sections, the utility of mRNA therapeutics is discussed for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines, cancer immunotherapy, and protein replacement therapy, followed by a discussion on the associated challenges.

SARS-CoV-2 Vaccines

mRNA-based therapeutics came to light with rapid development and emergency use authorization by the FDA during the COVID-19 pandemic. BioNTech in collaboration with Pfizer identified the initial vaccine candidate BNT162b2, which is a 5'-capped mRNA encoding the full-length spike protein of the SARS-CoV-2 virus (4). The mRNA is modified to include two proline mutations to increase protein expression stability. The mRNA also incorporated 1-methyl-pseudouridine, which suppresses the innate immune response and enhances in vivo mRNA translation. The vaccine is formulated in lipid nanoparticles, which supports uptake by cells upon intramuscular administration. The mRNA delivered into the cytoplasm is translated into modified viral spike protein, which upon subsequent proteasomal processing is presented on the cell surface leading to effective T-cell and B-cell responses. Subsequent phase I/II as well as large phase III trials ($n > 40\ 000$) revealed outstanding (95%) efficacy and safety profile of this vaccine (4). This made it the first vaccine against the SARS-CoV-2 virus to receive FDA emergency use authorization.

Similar to the BioNTech/Pfizer vaccine, the Moderna mRNA-1273 candidate encoding the spike protein of SARS-CoV-2 was identified early. mRNA-1273 also encodes a stabilized spike protein and is formulated in lipids for intramuscular delivery (4). Clinical trials revealed an efficacy of 94.5% and an excellent safety profile for this vaccine, which led to its FDA emergency use authorization shortly after the BioNTech/Pfizer vaccine. Another SARS-CoV-2 mRNA-based vaccine candidate that is undergoing phase III trials is CVnCov made by CureVac (4). Thus, the COVID-19 pandemic has accelerated the development of mRNA therapeutics and opened a new window of opportunity in the mRNA therapeutics domain.

Cancer Immunotherapy

The main utility of mRNA therapeutics in cancer is preventative vaccines (3). Many cancers harbor mutations, which lead to the generation of neoantigens that are recognized by the host immune system as foreign. Cancer vaccines aim to provide immunostimulation by inducing T- and B-cell responses against the tumor. In addition, mRNA may stimulate an innate immune response, leading to reduced immune tolerance against cancer (2, 3). Based on the mRNA delivery approach, cancer vaccines can be classified as either dendritic cell (DC) vaccines or direct vaccines. The antigens utilized for these vaccines can be tumor-associated self-antigens (TAAs) or tumor-specific antigens (TSAs). In the case of DC vaccines, one approach to delivering tumor antigens to the DCs is through isolation of bulk mRNA from autologous tumors and transfecting it to DCs ex vivo. These pulsed DCs are subsequently reinfused into the patient. This 'naked' mRNA delivery approach has shown safety and therapeutic benefit in phase I/II clinical trials for advanced melanoma (NCT01278940), wherein immune responders showed longer survival (14 vs 6 months) outcomes (2-4). However, since mRNA is extracted from individual tumors, the quality and availability of the vaccine may vary. In an alternative approach, mRNAs encoding defined TAAs can be produced in vitro and transfected into DCs. In a phase II clinical trial (NCT00965224) for acute myeloid leukemia, patients who were in remission were vaccinated with mRNA encoding Wilms' tumor (WT1) antigen. Forty-three percent of the patients displayed disease prevention or delayed relapse compared to historic controls (2-4). However, the overall clinical utility of DC vaccines is limited due to the need for isolation and cultivation of DCs ex vivo and reinfusions in patients, and T-cell responses may be relatively weak due to co-stimulation requirements.

Direct mRNA vaccines, as opposed to DC vaccines, are injected either intradermally or intranodally, wherein uptake by local DCs is expected to mount a T-cell immune response (1-4). Both nonformulated and formulated vaccines have been utilized. In the nonformulated approach, naked mRNA isolated from the tumor or IVT mRNA encoding defined TSAs is directly injected into the tissue. In a phase I trial of advanced melanoma patients, a TSA mRNA vaccine containing 20 defined mutations was administered (3). The vaccine was found to be safe, and the patients had sustained recurrence-free survival. A limitation of nonformulated vaccines is that intra- and extracellular RNases can rapidly degrade the mRNA, in turn causing a poor immune response. Formulations containing nanoparticles made of polymers such as protamine or cationic lipids protect mRNA molecules from RNase degradation. mRNA lipoplexes (RNA-LPX) utilizing cationic liposomes are promising due to their utilization in the BioNTech/Pfizer and Moderna vaccines against SARS-CoV-2. RNA-LPX-based mRNA vaccines encoding TAAs are currently being evaluated in phase I/II studies for several cancers, including triple-negative breast cancer (NCT02316457), as well as ovarian (NCT04163094), and prostate cancers (NCT04382898) (2-4). However, none of these potential therapeutics are approved by the FDA.

Protein Replacement Therapies

Protein replacement therapies (PRT) can be utilized to treat certain metabolic diseases, genetic disorders, and heart conditions (2, 4). However, due to the complexities and costs associated with producing recombinant proteins, PRTs are not available for many disorders. mRNA therapeutics, which can be easily designed and produced are being evaluated at the clinical level for a few conditions. mRNA-3705 is currently being evaluated in phase II clinical trials (NCT04899310) for treating methylmalonic acidemia (MMA) which is caused by the deficiency of methylmalonyl-CoA mutase (4). Similarly, mRNA-3927 producing propionyl-CoA carboxylase is being evaluated in phase II clinical trials (NCT04159103) for the treatment of propionyl acidemia (PA) (4). Both MMA and PA studies involve administering mRNA through the intravenous route. Another mRNA (MRT5005) under a phase II trial (NCT03375047) is for the treatment of cystic fibrosis caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) and utilizes a nebulizer to deliver the mRNA into the lung tissue (4). Last, AZD8601 naked mRNA, which encodes vascular endothelial growth factor (VEGF-A), is going through a phase II clinical trial (NCT03370887) to determine safety and efficacy in patients undergoing coronary artery bypass graft surgery (4). The AZD8601 is injected into the epicardium with the aim to promote local angiogenesis and improve systolic function. The main challenge associated with mRNA therapeutics in the setting of organ-specific protein deficiency is suboptimal targeted delivery. mRNA can also elicit an innate immune response or anti-mRNA humoral response, which is not desirable in the setting of protein deficiency disorders.

Common Challenges Associated with mRNA Therapeutics

The absorption, pharmacokinetics, excretion, and toxicity characteristics of mRNA drugs containing modified nucleotides (e.g., pseudouridine, 1-methylpseudouridine, and 2 fluoro-deoxyuridine), are not well known (2). This is a legitimate concern since certain nucleotides used in antiviral and anticancer treatments have shown mitochondrial toxicities causing adverse drug reactions (2, 5). The immune activation that results from mRNA administration needs assessment from a safety perspective, particularly when the therapeutic is being used for a nonimmune application. This is crucial since preclinical studies have reported upregulation of immune modulators such as interferon-α, interleukin-6, and tumor necrosis factor-α (2). In cases, where repetitive administration of specific mRNA is required, there is potential for the generation of self-RNA antibodies, which may result in autoimmunity (2). Therefore, clinical monitoring of autoimmune conditions may be required.

Conclusion

The emergency use authorization of two mRNA-based vaccines in less than a year has dramatically improved our understanding of their safety and efficacy. This advancement is likely to positively impact the development of mRNA-based cancer vaccines and protein replacement therapies. Longitudinal studies on the amount of protein production and immune response are ongoing and will provide insight into the length of the effective immune response.

Learning Objectives

After reading this article, the reader will be able to explain the basis of mRNA therapeutics and list advantages over DNA and protein-based therapeutics. The reader will be able to describe the clinical utility of mRNA therapeutics in COVID-19, cancer immunotherapy, and protein replacement therapies.

References

1. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines — a new era in vaccinology. Nat Rev Drug Discov 2018;17:261–79.
2. Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics — developing a new class of drugs. Nat Rev Drug Discov 2014;13:759–80.
3. Beck JD, Reidenbach D, Salomon N, Sahin U, Türeci Ö, Vormehr M, Kranz LM. mRNA therapeutics in cancer immunotherapy. Mol Cancer 2021;20:69.
4. Damase TR, Sukhovershin R, Boada C, Taraballi F, Pettigrew R, Cooke J. The limitless future of RNA therapeutics. Front Bioeng Biotechnol 2021;9:628137.
5. McKenzie R, Fried MW, Sallie R, Conjeevaram H, Di Bisceglie AM, Park Y, et al., Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B. N Engl J Med 1995;333:1099–105.

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Stimulants – A New Wave of Drug Abuse

By Heather A. Nelson, PhD

Stimulants are a class of drugs that includes both illicit drugs, such as methamphetamine and

cocaine, and prescription stimulants, such as dextroamphetamine and methylphenidate. These drugs increase alertness, attention, energy, blood pressure, heart rate, and respiration. They act on monoamine neurotransmitter systems in the brain to increase norepinephrine and dopamine. These monoamines are responsible for the sympathetic response to stress, metabolic changes in response to fear, and euphoric sensations. While the opioid overdose epidemic took center stage in the 2010s, abuse of stimulants has also been steadily on the rise since 2010. In the US, from 2016 to 2017, there was a 37% increase in overdose deaths involving stimulants, with more than 10 000 reported deaths (1). While deaths involving cocaine have been the leading cause of stimulant related deaths for many years, there is a shift toward deaths involving other stimulants, such as methamphetamine (Figure 1).

Methamphetamine is one of the most widely abused illicit psychostimulants; in 2017, more than 14.7 million people had tried methamphetamine at least once (2). It rapidly enters the brain and directly affects the central nervous system (CNS) by stimulating rapid release of dopamine, causing increased activity and talkativeness, decreased appetite, and a pleasurable sense of well-being. Methamphetamine can be administered multiple different ways, including smoked, snorted, injected, or orally ingested, and the physiological effects are felt rapidly and can last for several hours, contributing to its addictive properties (3). Taken acutely, methamphetamine accelerates heart and lung activity, increases release of stress hormones, and slows non-essential functions, such as digestion. Chronic exposure or overstimulation of methamphetamine can cause severe cardiovascular complications and cognitive deficits. In 2017, about 15% of all drug overdose deaths involved methamphetamine. It is important to note that about 50% of those deaths also involved an opioid, highlighting a rise in polysubstance abuse disorder (2). Less commonly, illicit methamphetamine may be contaminated with synthetic opioid impurities, which were detected in approximately 2% of nearly 300 000 methamphetamine substance reports made in 2017 (4).

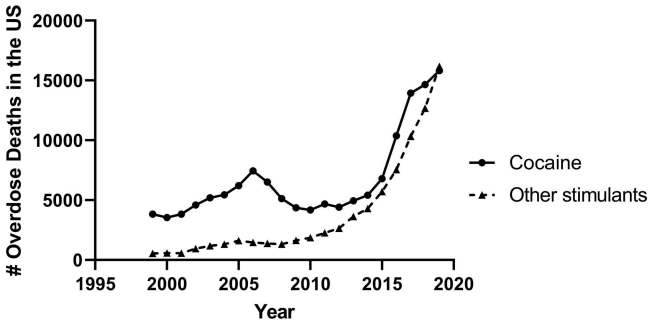

Figure 1. Age-adjusted rates of drug overdose deaths involving stimulants in the United States, 1999–2019. *Other stimulants* include stimulants with abuse potential such as methamphetamine, amphetamine, and methylphenidate. Deaths may involve more than one drug. Data from: https://www.cdc.gov/nchs/data/databriefs/db394-tables-508.pdf#4. SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality (8).

Stimulant prescriptions have also dramatically increased in the last 20 years, particularly for amphetamines, leading to greater availability and increased risk for misuse. While increases in prescription of amphetamines to children for treatment of attention deficit hyperactivity disorder (ADHD) have begun to level off, prescriptions for adults have continued to rise, including prescriptions for off label uses, such as weight loss. In 2015 and 2016, approximately 6.6% (16 million) adults in the United States used prescription stimulants (5). According to data from National Surveys on Drug Use and Health, about 31.2% of these prescription drug users report misusing the medication at least once (5). The most common source of prescription stimulant misuse was taking drugs prescribed to family or friends, suggesting an ongoing issue of prescription diversion.

Urine drug screening is used to monitor adherence to prescription pain medication and can help combat prescription diversion. Amphetamines are included on most urine drug screens. The initial screen is most commonly done by immunoassays, which are designed to detect dextroamphetamine, or dextromethamphetamine, with lesser, but still significant, cross-reactivity for levo-enantiomers. If monitoring compliance for prescribed amphetamines, they are generally detectable in urine for approximately 2 days (6). These tests cannot distinguish between prescription drug use and illicit formulations. Additionally, the immunoassays are subject to false-positive results from chemically related compounds. Unexpected positive results should be confirmed by more specific methods, such as liquid-chromatography tandem mass spectrometry.

Stimulant drug use is a widespread problem, carrying significant societal costs. While programs and effective treatment options have been developed surrounding the opioid epidemic, less proven treatments and interventions have focused on stimulant use disorder. Bupropion and naltrexone

individually have shown some efficacy in treating methamphetamine use disorder in clinical trials; however, a recent study investigating the efficacy of combining these agents to treat methamphetamine abuse disorder showed only modest effectiveness of the treatment (7). As stimulant use continues to climb, it will be important to address this trend in drug abuse to mitigate another drug crisis.

Learning Objectives

After reading this article, the reader will be able to describe the current trends in stimulant abuse and understand how methamphetamine use can lead to health deficits and overdose deaths.

References

1. Opioid Overdose: Other Drugs. https://www.cdc.gov/drugoverdose/data/otherdrugs.html (Accessed February 2021).
2. NIDA. How is methamphetamine different from other stimulants, such as cocaine? https://www.drugabuse.gov/publications/research-reports/methamphetamine/ (Accessed February 2021).
3. Panenka WJ, Procyshyn RM, Lecomte T, MacEwan GW, Flynn SW, Honer WG, et al. Methamphetamine use: A comprehensive review of molecular, preclinical and clinical findings. Drug Alcohol Depend 2013;129: 167–79.
4. Jones CM, Bekheet F, Park JN, Alexander GC. The evolving pverdose epidemic: Synthetic ppioids and rising stimulant-related harms. Epidemiol Rev 2020;42: 154–66.
5. Compton WM HB, Blanco C, Johnson K, Jones CM. Prevalence and correlates of prescription stimulant use, misuse, use disorders, and motivations for misuse among adults in the United States. Am J Psychiatry 2018;175: 741–55.
6. Moeller KE, Lee KC, Kissack JC. Urine drug screening: Practical guide for clinicians. Mayo Clin Proc 2008;83: 66-76.
7. Trivedi MH, Walker R, Ling W, dela Cruz A, Sharma G, Carmody T, et al. Bupropion and naltrexone in methamphetamine use disorder. N Engl J Med 2021;384: 140–53.
8. National Center for Health Statistics. Public-use data files: Mortality multiple cause files. 2019. Available from: https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm#Mortality_Multiple.

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Learning Objectives

Learning objectives vary by article, but in general, after completing *Clinical & Forensic Toxicology News*, the reader will be able to:

- Describe emerging and changing trends in drug abuse, including new designer drugs, usage patterns, and contaminants/adulterants.
- Identify potential analytes (drugs, metabolites, biomarkers) of clinical and/or forensic significance.
- Evaluate methodologies for their utility and limitations relative to the needs of toxicology labs.
- Discuss relevant regulations, such as analytical performance requirements, or the legality of new drugs of abuse.
- Explain the analytical and regulatory issues unique to specific applications, including postmortem toxicology, workplace drug testing, and drug screening.
- Describe the medical implications of drug abuse, toxicity associated with therapeutic agents, and exposure to other toxicants.

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