Urine Drug Tests: Ordering and Interpretation

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Urine drug testing is an essential component of monitoring patients who are receiving long-term opioid therapy, and it has been suggested for patients receiving long-term benzodiazepine or stimulant therapy. Family physicians should be familiar with the characteristics and capabilities of screening and confirmatory drug tests. Immunoassays are qualitative tests used for initial screening of urine samples. They can give false-positive and false-negative results, so all results are considered presumptive until confirmatory testing is performed. Immunoassays for opioids may not detect commonly prescribed semisynthetic and synthetic opioids such as methadone and fentanyl; similarly, immunoassays for benzodiazepines may not detect alprazolam or clonazepam. Immunoassays can cross-react with other medications and give false-positive results, which have important implications for a patient's pain treatment plan. False-negative results can cause missed opportunities to detect misuse. Urine samples can be adulterated with other substances to mask positive results on urine drug testing. Family physicians must be familiar with these substances, the methods to detect them, and their effects on urine drug testing. (*Am Fam Physician*. 2019;99(1):33-39. Copyright © 2019 American Academy of Family Physicians.)

Urine drug testing is an important part of managing long-term opioid therapy. With the recent increase in deaths caused by opioid overdoses, several federal and state regulations have been enacted that recommend or require urine drug testing in patients receiving long-term opioid therapy. Similar guidance has been suggested for patients receiving long-term benzodiazepine or stimulant therapy. The purpose of urine drug testing is to monitor compliance with prescribed therapy and detect the use of nonprescribed and illicit substances, especially heroin and nonprescribed opioids and benzodiazepines, all of which can increase the risk of a fatal overdose.[1,2] Weak evidence suggests that random urine drug testing decreases the use of illicit drugs in patients receiving long-term opioid therapy.[3]

Additional content at https://www.aafp.org/afp/2019/0101/p33.html.

CME **This clinical content** conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 11.

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A positive urine drug test result has significant implications for a patient's pain treatment plan, as well as his or her personal and professional life. Many controlled substance treatment agreements specify that pain medications will be tapered off or stopped if a test result is positive. Some state regulatory agencies require consultation with a pain management subspecialist if misuse is suspected[4]; therefore, it is imperative that family physicians know how to order urine drug tests and interpret results.

Family physicians cannot rely on urine drug testing alone to determine adherence to therapy, nor can testing reliably detect intermittent use of nonprescribed substances. Because there are no typical behaviors that predict misuse or diversion, monitoring of patients receiving long-term opioid therapy should include a focused history using validated tools (e.g., Opioid Risk Tool, Addiction Behaviors Checklist, Pain Medication Questionnaire), physical examination, and use of prescription drug monitoring programs. Before ordering a urine drug test, the physician must note when the patient last took a prescription medication (to determine the likelihood of a positive test result), whether any other medications were taken

WHAT IS NEW ON THIS TOPIC

Urine Drug Testing

Several federal and state regulations have been enacted that recommend or require urine drug testing in patients receiving long-term opioid therapy. Similar guidance may apply to patients receiving long-term benzodiazepine or stimulant therapy.

Ingestion of food containing poppy seeds will not cause a positive urine drug test result. Similarly, passive inhalation of marijuana smoke is unlikely to cause a positive tetrahydrocannabinol urine test result.

concurrently (that might cross-react with the assay), and whether any nonprescribed or illicit substances were used (in the event of an unexpected positive result). The physician must also be aware of which substances are most commonly misused in the community.

Frequency of Testing

Guidelines from the American Pain Society[5] and the Centers for Disease Control and Prevention[1] on the use of long-term opioid therapy for chronic noncancer pain recommend periodic urine drug testing for adherence to treatment, but the frequency is left to the individual physician. More frequent testing is required for patients at high risk of misuse and those with aberrant behaviors.[1] *Table 1* lists suggested frequencies for urine drug testing based on individual risk factors.[6]

Choosing the Correct Test

Urine, serum, saliva, sweat, and hair can be tested for the presence of drugs. However, urine testing is most common because of ease of collection, adequate sensitivity and specificity to detect commonly used drugs, and a longer window of detection than serum.[7] Urine drug concentrations do not reflect serum concentrations; rather, they are a function of how rapidly a person metabolizes and eliminates the drug and its metabolites, as well as hydration status. Urine drug testing can be performed in the office as a point-of-care test, or the sample can be sent to a reference laboratory for testing. Testing may be performed for reasons other than monitoring opioid therapy,[8] such as drug rehabilitation, employment requirements (e.g., for occupations that require special transportation licensing), military or sports participation, or legal situations. Properly performed urine drug testing involves two steps: an initial screening test followed by confirmatory testing for substances with positive screening results. Confirmatory testing is also needed in situations with an unexpected negative result as a means of distinguishing a false negative from a true negative.[9]

The initial screening test is usually an immunoassay, a qualitative test that screens for the five major drug classes targeted by federal workplace testing programs: opioids, cannabinoids, cocaine, amphetamines, and phencyclidine. Immunoassays can be performed at the point of care, provide rapid results, and are relatively inexpensive. Positive and unexpected negative samples are then sent to a reference laboratory for confirmatory testing. Immunoassays can also be sent to a reference laboratory with instructions to run confirmatory tests.

Specific immunoassays must be ordered for different substances; therefore, physicians should be familiar with the test used in their office and at the reference laboratory they routinely use. The typical immunoassay can detect only nonsynthetic opioids (morphine and codeine). The immunoassays used for workplace testing programs are useful for detecting illicit substances such as cannabis or cocaine, but they do not reliably detect synthetic

TABLE 1

Recommended Frequency for Urine Drug Testing

Level of misuse risk	Frequency
Low (no risk factors)	Every 6 to 12 months
Moderate	Every 3 to 6 months
High (mental health disorder, substance use disorder, prior opioid misuse, aberrant behavior*) or opioid dosage > 120 morphine milligram equivalents	Every 1 to 3 months

*—Aberrant behavior includes but is not limited to lost prescriptions, multiple requests for early refills, opioid prescriptions from multiple physicians, unauthorized dose escalation, and apparent intoxication.

Adapted with permission from Washington State Agency Medical Directors' Group. Interagency guideline on prescribing opioids for pain. 3rd ed. June 2015. http://www.agencymeddirectors.wa.gov/files/2015amdgopioidguideline.pdf. Accessed August 18, 2018.

or semisynthetic opioids (e.g., methadone, buprenorphine, oxycodone, oxymorphone, fentanyl) or help distinguish between various opioids. Therefore, many laboratories require a specific order to test for semisynthetic and synthetic opioids and other drugs such as carisoprodol (Soma). Immunoassays that test for the presence of other common prescription drugs, such as benzodiazepines, are also available. Many benzodiazepine immunoassays reliably detect nordiazepam (metabolite of diazepam [Valium]), oxazepam, and temazepam (Restoril), but not alprazolam (Xanax), lorazepam (Ativan), or clonazepam (Klonopin).[10] Hence, a positive screening result must always be followed with confirmatory testing. Furthermore, if benzodiazepine use is suspected, the sample must be sent for additional testing despite a negative initial screening result.

Most confirmatory tests use gas or high-performance liquid chromatography to separate various drugs, and mass spectrometry to detect them. These methods have a much lower threshold for detection and are able to accurately distinguish individual drugs and metabolites. Because of cost constraints, it is not practical to test each sample for every possible drug. The physician should be aware of which tests to order if nonadherence or substance misuse is suspected. The initial test should include the prescribed drug, amphetamines, opioids, cocaine, benzodiazepines, oxycodone, barbiturates, methadone, fentanyl, and marijuana.[6] *Table 2* lists commonly

TABLE 2

Commonly Ordered Drug Tests, Windows of Detection, and Analytes

Test	Window of detection[11-14]	Analytes[13,15,16]
Amphetamines	2 to 3 days	Amphetamine, methamphetamine, methylenedioxyamphetamine, methylenedioxymethamphetamine
Benzodiazepines*		Alpha-hydroxyalprazolam, 7-aminoclonazepam, oxazepam
Short acting	3 to 5 days	
Long acting	Up to 30 days	
Buprenorphine	Up to 11 days	Norbuprenorphine
Cannabis		11-nor-9-carboxy-tetrahydrocannabinol
Single use	2 days	
3 times per week	2 weeks	
Daily use	2 to 4 weeks	
Very heavy use	4 to 6 weeks (up to 12 weeks)	
Cocaine	1 to 5 hours (2 to 4 days for metabolites)	Benzoylecgonine, ecgonine methyl ester
Codeine	1 to 2 days	Hydromorphone, morphine
Fentanyl	2 to 3 days	Norfentanyl
Heroin and morphine	3 days	Codeine, hydromorphone, 6-monoacetylmorphine, morphine
Hydromorphone (Dilaudid)	1 to 2 days	Hydromorphone
Methadone	3 to 4 days (up to 14 days)	2-ethylidene-1,5-dimethyl-3, 3-diphenylpyrrolidine
Oxycodone		Noroxycodone, noroxymorphone, oxycodone, oxymorphone
Immediate release	1 to 1.5 days	
Controlled release	1.5 to 3 days	
Oxymorphone		Noroxymorphone, oxymorphone
Immediate release	1.5 to 2.5 days	
Controlled release	1 to 4 days	
Phencyclidine	1.5 to 10 days	Phencyclidine
Tapentadol (Nucynta)	1 to 5 days	Tapentadol, tapentadol O-sulfate
Tramadol	2 to 4 days	Nortramadol
Zolpidem (Ambien)	1 to 5 days	Zolpidem

*—High dosages may give positive test results for up to 6 weeks.

Information from references 11 through 16.

ordered tests, the principal drug analytes they detect, and their windows of detection.[11-16]

Recently, several synthetic cannabinoids (e.g., spice), cathinones (e.g., bath salts), and hallucinogens (25I-NBOMe or N-bomb) have been sold as "legal stimulants" as a way to avoid regulatory controls.[17,18] The manufacturers vary the chemical composition of these drugs, and most commercial urine drug tests are not able to detect them. If the patient's symptoms suggest ingestion of these drugs, urine and blood samples should be sent to laboratories that are capable of detecting them.

Interpreting Test Results

Many drugs are rapidly metabolized into active or inactive metabolites. Drug testing is dependent on detecting these metabolites. Opioids and benzodiazepines include multiple drugs with overlapping metabolic pathways, which can make interpretation of screening results difficult *(eFigures A and B)*. Thus, the presence of morphine in a sample could indicate morphine, codeine, or heroin use, or any combination of these. Similarly, the presence of hydromorphone (Dilaudid) could indicate hydromorphone, hydrocodone, or morphine use.

False-positive results can occur from cross-reactivity of commonly used medications with the assay. This a particular concern with immunoassays. *Table 3* lists common medications that can cause false-positive results on urine drug testing.[9] Negative results are particularly difficult to interpret, especially when a patient is receiving long-term opioid therapy and the physician expects a positive result. True-negative results occur when a patient is not taking the medication as prescribed and there is no drug present in the urine sample, or when the drug is metabolized so rapidly that the metabolites are eliminated before they can be detected. False-negative results occur when a drug or metabolite is present at such low levels that it is not detected. Confirmatory testing is essential to distinguish a true negative from a false negative. Contaminants can also interfere with the immunoassay's ability to detect the presence of drugs.

The use of heroin with concurrent prescription opioids is also a cause for concern. Although both substances will give a positive result for opioids, the presence of 6-monoacetylmorphine indicates heroin use. This metabolite has a short

TABLE 3

Common Medications That Can Cause False-Positive Results on Urine Drug Testing

Drug	Cross-reactive medications/substances
Amphetamines	Amantadine, benzphetamine (Regimex), bupropion (Wellbutrin), chlorpromazine, clobenzorex (not available in the United States), desipramine, dextroamphetamine, ephedrine (Akovaz), fenproporex (not available in the United States), isometheptene (component of Prodrin), labetalol, levomethamphetamine (active ingredient in some over-the-counter nasal decongestant inhalers), methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), methylphenidate (Ritalin), phentermine (Adipex-P), phenylephrine, promethazine, pseudoephedrine, ranitidine (Zantac), selegiline (Eldepryl), thioridazine, trazodone, trimethobenzamide (Tigan), trimipramine (Surmontil)
Benzodiazepines	Oxaprozin (Daypro), sertraline (Zoloft)
Cannabinoids	Dronabinol (Marinol), efavirenz (Sustiva), hemp-containing foods, proton pump inhibitors, tolmetin and other nonsteroidal anti-inflammatory drugs
Cocaine	Coca leaf tea, topical anesthetics containing cocaine
Opioids	Dextromethorphan, heroin, quinine, quinolones, rifampin, verapamil
Phencyclidine	Dextromethorphan, diphenhydramine (Benadryl), doxylamine, ibuprofen, ketamine (Ketalar), meperidine (Demerol), thioridazine, tramadol, venlafaxine

Adapted with permission from Smith MP, Bluth MH. Common interferences in drug testing. Clin Lab Med. *2016;36(4):665-666.*

half-life, however, with a window of detection in urine of approximately two to eight hours. Acetylated-thebaine-4-metabolite glucuronide is a metabolite of thebaine, which is found in street heroin; it has been proposed as a new marker to differentiate morphine and codeine ingestion from heroin use.[19,20] If concurrent opioid and heroin use is a concern, the pathologist or toxicologist at the local reference laboratory should be consulted to determine the appropriate ordering and testing procedure.

TABLE 4

Adulterants Used to Prevent Detection of Drugs in Urine Samples

Adulterant	Composition	Mode of action
Ammonia	Ammonia	Interferes with detection of benzoylecgonine and phencyclidine
Bleach	Sodium hypochlorite	Interferes with immunoassay; may cause degradation of analyte for gas chromatography
Goldenseal (*Hydrastis canadensis*)	Herbal diuretic	Dilution to below cutoff level; decreases immunoassay sensitivity to amphetamines and THC
Klear, Whizzies	Potassium nitrite	Interferes with THC immunoassay and gas chromatography/mass spectrometry analysis
Powdered urine	Dried human urine residue	Substitution
Stealth	Peroxide and peroxidase	Interferes with THC and opioid immunoassays
Urinaid, Clean-X	Glutaraldehyde	Decreases immunoassay sensitivity to multiple drugs
Urine Luck, Instant Clean Add-it-ive	Pyridinium chlorochromate	Strong oxidizing agent; interferes with immunoassay and gas chromatography/mass spectrometry analysis for multiple drugs
Vinegar	Acetic acid	Decreases immunoassay sensitivity to THC
Visine eye drops	Benzalkonium chloride	Decreases immunoassay sensitivity to THC
Water plus diuretics	—	Dilution to below cutoff level

THC = tetrahydrocannabinol.

Information from references 15 and 21.

Tampering and Contamination of Urine Samples

Urine samples are sometimes contaminated deliberately by ingestion or addition of a foreign substance to prevent detection of illicit drugs. Common methods of tampering include dilution with water, addition of extraneous substances, or substitution of samples. *Table 4* lists commercially available agents marketed to help disguise the presence of illicit drugs in urine samples.[15,21] Many laboratories now routinely check urine creatinine levels to determine whether the sample is excessively dilute and to check for the presence of adulterants. Several commercially available point-of-care systems check for the presence of adulterants in addition to the substances being tested for.[21] Although these systems can detect adulterants, they cannot determine which substances are being concealed. The practice known as shaving can also confound drug test results: a patient who is not taking the prescribed drug will add a small amount of the drug directly to the urine specimen to avoid having a negative test result. In these cases, the urine will test positive for the drug—often at a high concentration—but not for its metabolite. Such results should raise suspicion of medication nonadherence. *Table 5* lists possible unexpected results from urine drug tests and potential causes.

Unintentional Ingestions and Exposures

Ingestion of poppy seeds is sometimes claimed as a reason for an unexpected positive opioid test result. To study this claim, researchers recruited

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Urine drug testing can be used to monitor compliance with prescribed therapy and detect the use of nonprescribed and illicit substances, especially opioids, benzodiazepines, and heroin.	C	1
Immunoassays are subject to false-positive and false-negative results. All positive and any unexpected negative results must be verified by confirmatory testing.	C	9
Casual dietary ingestion of poppy seeds does not cause a positive result for opioids on urine drug testing.	C	22
Casual exposure to cannabis smoke does not cause a positive result on urine drug testing.	C	23

A = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to https://www.aafp.org/afpsort.

15 volunteers to consume a poppy seed roll and raw poppy seeds before undergoing urine and oral fluid drug testing.[22] Although the tests did detect morphine and codeine in the samples, the levels were far below the cutoff for commercial testing. Therefore, casual ingestion of a poppy seed–containing food will not cause a positive test result. Similarly, passive inhalation of marijuana smoke has been claimed as a cause for a positive tetrahydrocannabinol (THC) test result. Studies have shown that although casual passive inhalation of marijuana smoke does cause elimination of THC in urine samples, the amount excreted is far below the federal and commercial cutoffs for testing and should not cause a positive test.[23] Extreme exposure and high room air concentrations of THC were required to cause positive urine screening results in test participants.

TABLE 5

Possible Causes for Unexpected Results on Urine Drug Tests

Result	Possible cause
Illicit substance present	Illicit substance use, false-positive result due to cross-reactivity
Low creatinine level and specific gravity	Deliberate dilution of urine; low body mass, renal dysfunction
Nonprescribed drug present	Nonmedical use of prescription medication; false-positive result due to cross-reactivity
Prescribed drug absent	True negatives: patient has not taken medication in the detection window; rapid metabolizer False negatives: urine concentrations below cutoff levels; contaminant present that interferes with test
Prescribed drug present in high concentration and/or metabolites absent	Recent dosing; concentrated urine (high creatinine level); unsanctioned dose escalation; concurrent use of prescription and illicit substances; "shaving" (i.e., adding a small amount of drug to the urine to demonstrate compliance)

Cost of Urine Drug Testing

As more persons are required to undergo urine drug testing for monitoring long-term opioid therapy, the cost of testing and coverage by third-party payers are considerations that should be taken into account. Some insurers limit the number of tests they will cover in a year, and others do not pay for urine drug testing at all. The out-of-pocket cost for urine drug testing varies greatly depending on geographic region and the laboratory used. A popular health care cost comparison website lists the fair price for a urine drug screen as $128, with a range of $62 to $308.[24] Medicare covers testing for patients with an appropriate indication; reimbursement ranges from $13 to $72 for the initial immunoassay, depending on the test used.[25]

This article updates a previous article on this topic by Standridge, et al.[8]

Data Sources: PubMed was the primary data source used. Multiple searches were conducted using the terms urine drug tests, urine drug screen, pharmacokinetics, metabolism plus the individual drug names, urine drug screen adulterants, and urine drug screen interpretation. Google Scholar, the Cochrane database, and the websites for the Agency for Healthcare Research and Quality and U.S. Preventive Services Task Force were also searched. Search dates: September 2017, and January and April 2018.

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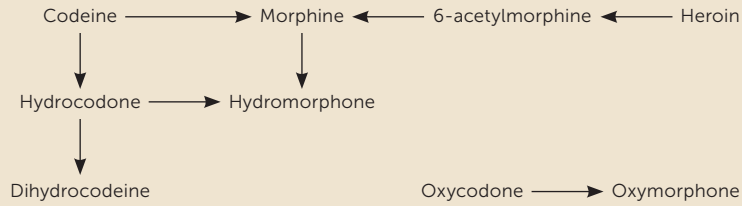
eFIGURE A



Metabolic pathways of opioids.

Information from:

Reisfield GM, Chronister CW, Goldberger BA, Bertholf RL. Unexpected urine drug testing results in a hospice patient on high-dose morphine therapy. Clin Chem. *2009;55(10):1766.*

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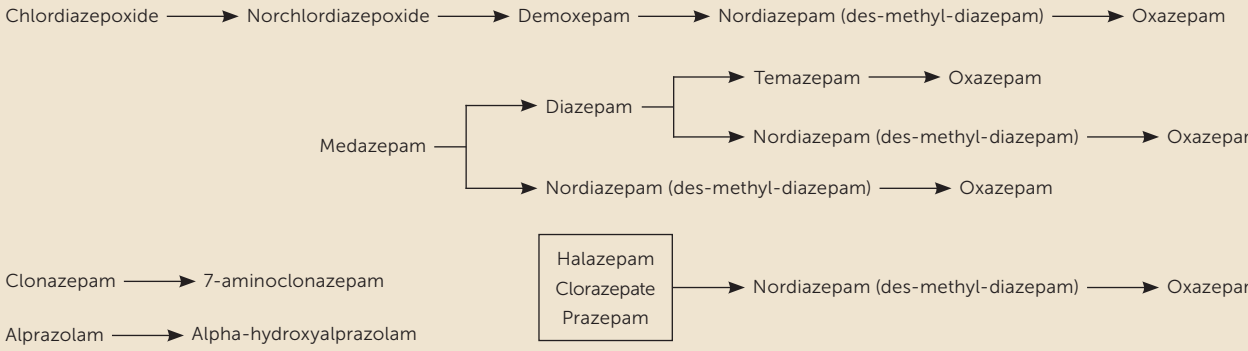
eFIGURE B



Metabolic pathways of benzodiazepines.

Information from Valentine JL, Middleton R, Sparks C. Identification of urinary benzodiazepines and their metabolites: comparison of automated HPLC and GC-MS after immunoassay screening of clinical specimens. J Anal Toxicol. *1996;20(6):419.*

VIEWPOINT

Medication-Based Treatment to Address Opioid Use Disorder

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The opioid epidemic was declared a national public health emergency on October 26, 2017, and, although there have been some significant increases in federal funding and new programs to address this crisis, progress appears to be slow and the United States continues to be severely affected by substance use disorder.[1] As of 2016, approximately 2 million individuals in the United States have been diagnosed with opioid use disorder (OUD),[1] and an estimated 130 people die every day from a drug overdose.[2] To reverse these unacceptable trends, all evidence-based tools must be utilized. Specifically, medication-based treatment, which has been proven to be effective in treating substance use disorder and saving lives, has been severely underutilized for decades. According to 2019 estimates, "less than 35 percent of adults with OUD had received treatment for opioid use in the past year and no national data sources are currently available to precisely estimate the share of those patients who are being treated with one of the three US Food and Drug Administration (FDA)-approved medications."[1]

Medication-based treatment for OUD includes the use of methadone, buprenorphine, or extended-release naltrexone to "alleviate withdrawal symptoms, reduce opioid cravings, and decrease the response to future drug use."[1] These medications are approved for use by the FDA and there is strong evidence of their effectiveness and scientific consensus that medications are central to the management of OUD. Medication-based treatment is not only effective in supporting safe and less agonizing withdrawal, but it also reduces mortality and promotes increased functionality in the family, community, and society. For example, studies have shown that maintenance programs that use medication-based programs decrease mortality by approximately 50%[3] and that while individuals are being treated with medications, overall rates of criminal convictions were reduced to less than half of pretreatment levels.[4] According to a 2019 report from the National Academies of Sciences, Engineering, and Medicine, patients who receive medication-based treatment are "less likely to die from overdose if they return to use…have better long-term treatment outcomes, and improved social functioning."[1]

> Opioid use disorder is a chronic brain disease, not simply a moral failing.

Despite their demonstrated success, these medications are inadequately used. In addition, there are challenges in ensuring that individuals who need treatment seek it out; only 4.5% of individuals who could benefit from substance abuse treatment feel that they need it.[5] Even when medication-based treatments are used, they are often administered in doses below the recommended level, reducing their effectiveness. As the United States confronts the devastating opioid crisis, why are clinicians, treatment centers, and individuals who help address OUD not utilizing these evidence-based, proven solutions?

One reason is widespread misunderstanding and stigma surrounding both substance use disorder and the medications used to manage it. OUD is a chronic brain disease, not simply a moral failing. Opioid use changes brain structure and function in ways that "disrupt the regulation of the system and result in tolerance, physical dependence, and addiction."[1] Evidence has borne out that medication-based treatment can assist in compensating for some of these changes in the brain.

Moreover, misunderstanding has led clinicians to be slow to utilize these medication-based treatments, often only prescribing them alongside behavioral and social interventions and forgoing medication-based treatment if these nonpharmacologic interventions are not also available. Clinicians need to break the inextricable coupling of medication-based treatment with behavioral and social treatment and understand that these interventions are addressing 2 separate aspects of substance use disorders. While behavioral and social interventions are extremely useful for some patients and can help with engagement in and retention of treatment, medication-based treatment alone can be effective for many patients. Therefore, the lack of access to social and behavioral therapies should not be used as a reason to withhold medical treatment. It is better for patients to receive medication-based treatment alone than not at all.

Patients have also reported stigmatizing attitudes across the health sector toward both themselves and these medications. Some clinicians report their unwillingness to prescribe these medications because of misplaced concerns about misuse and diversion and "the public's mistaken belief that taking medication is 'just substituting one drug for another.'"[1]

It is an inexcusable error that evidence-based interventions exist but are not used for patients with OUD. Clinicians need to overcome any personal biases and provide patients with OUD the necessary care to help them recover.

To help advance scientific, evidence-based solutions to the opioid crisis, the 2019 report from the National Academies of Sciences, Engineering, and Medicine provides a road map toward ensuring that medication-based treatment for OUD becomes more

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broadly deployed. The report puts the issue in stark terms and states "Withholding or failing to have available all classes of FDA-approved medication for the treatment of opioid use disorder in any care or criminal justice setting is denying appropriate medical treatment."[1] These treatments are efficacious across all populations studied (including adolescents, pregnant women, and individuals under criminal justice control). Clinicians need to ensure that individuals who need these treatments have access to them.

It also is critical that medication-based treatment for patients with OUD becomes available across treatment settings, including acute care, residential facilities, and primary care. Currently, methadone can only be distributed through specialty facilities despite evidence showing that its distribution through office settings is also safe and effective.[1] Many residential treatment centers do not offer any medication-based treatment for OUD and, of those that do, only a fraction offer all 3 medications.

Other systemic barriers also hinder access to and use of these treatments. Patients experience a confusing web of clinicians, levels of care, interventions, and insurance coverage when they try to access treatment for OUD. Education about management of OUD is not standardized within or across the health professions, leaving a limited number of clinicians who are comfortable treating patients with OUD. In addition, few clinicians want to treat patients with OUD because they are sporadically reimbursed from both public and private insurance for this work. Also, although effective medication-based treatments exist, research should continue to establish specific protocols for different populations, identify complementary interventions that can be implemented alongside medication-based treatment, and search for additional more efficacious medication-based treatments. The epidemic is not abating; the medical and public health communities must continue to push forward on all fronts.

Seventeen months after the declaration of a public health emergency, it may seem as though the United States is no further along than when the declaration was issued, and in many ways that is true. But effective solutions are available. Medication-based treatments can save lives. They need to be used.

ARTICLE INFORMATION

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Proceedings of a Workshop

IN BRIEF

November 2018

Medication-Assisted Treatment for Opioid Use Disorder

Proceedings of a Workshop—in Brief

On October 30 and 31, 2018, the Committee on Medication-Assisted Treatment (MAT) for Opioid Use Disorder (OUD) held a 1.5-day workshop in Washington, DC. To support the dissemination of accurate patient-focused information about treatments for addiction, and to help provide scientific solutions to the current opioid crisis, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was created to conduct a study of the evidence base on MAT for OUD. Specifically, the committee was asked to (1) review the current knowledge and gaps in understanding regarding the effectiveness of MAT for treating OUD, (2) examine the available evidence on the range of parameters and circumstances in which MAT can be effectively delivered (e.g., duration of treatment, populations, settings, and interventions to address social determinants of health as a component of MAT), (3) identify challenges in implementation and uptake, and (4) identify additional research needed. The public workshop was designed to assist the committee in gathering evidence, as well as to bring the committee together with a wide range of clinicians, academic experts, policy makers, and representatives of affected individuals and family members for a full discussion of the current initiatives related to MAT, existing evidence and research gaps, and barriers that discourage access to and use of MAT.

This Proceedings of a Workshop—in Brief highlights the presentations and discussions that occurred at the workshop. It should not be seen as reflecting findings, conclusions, or recommendations of the workshop participants or of the committee. Statements, proposals, and opinions expressed are those of individual presenters and participants and have not been endorsed or verified by the National Academies or the committee and they should not be construed as reflecting any group consensus. The committee's Consensus Study Report will be available in spring 2019.

FEDERAL INITIATIVES

The first session focused on the current federal efforts to improve treatment for OUD and access to MAT. Committee members heard the perspectives of two speakers from the agencies sponsoring the study—the National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA)—as well as from other federal agencies also working in this domain: the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA), and the Food and Drug Administration (FDA).

Nora Volkow, director of NIDA, emphasized that OUD is rapidly lethal, killing 2 percent of the 2.1 million people with OUD in the United States each year. Medications are irrefutably the most effective way to treat OUD—reducing the likelihood of overdose death by up to three-fold—but fewer than half of patients receive them due to stigma and structural barriers, and treatment retention is poor, she said. NIDA is focusing on implementation science and service delivery research to expand access to MAT in the health care and criminal justice systems. Priority knowledge gaps include the effectiveness of different MAT modalities across the continuum of OUD severity, optimal duration of MAT, impact of individual factors, and transition off MAT. Volkow maintained that evidence should guide decisions about the type of MAT that is biologically optimal for an individual. She explained that OUD is highly heterogeneous,

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with outcomes shaped by disease severity and the environmental factors, thus patients need support systems to stay in treatment. Volkow remarked that educating all providers about treating OUD is low-hanging fruit. She pointed to insurance and reimbursement problems—as well as the traditional methadone clinic model—as key structural barriers to implementing MAT. She also added that a wider segment of the pharmaceutical industry should be engaged to develop better medications for treating OUD.

Deepa Avula of SAMHSA described how the agency is working to improve MAT service delivery. The State Opioid Response Grants program supports the development of comprehensive care systems for OUD with the flexibility for states to tailor system design to their specific needs and available resources. She noted that SAMHSA strengthened the language around the requirement that programs make MAT available. SAMHSA also engages peers with lived experience to help people with OUD to rebuild their lives and funds public awareness campaigns and extensive OUD-specific training and technical assistance. She said that SAMHSA is rolling out a program to embed buprenorphine-waiver training[1] within medical school curricula to expand access to the medication. She contended, "if every waivered physician were to serve patients even anywhere close to their limit, we would not have an opioid crisis in this country." Avula suggested conducting population-specific research to examine the comparative effectiveness of different care models for people with co-occurring conditions. She also highlighted the importance of community supports to complement medication across the spectrum of care.

Molly Evans outlined CDC's OUD-related activities: conducting surveillance and research; building state, local, and tribal capacity for prevention; supporting providers, health systems, and payers with guidance about opioid prescribing practices; partnering with public safety organizations on prevention strategies in high-intensity drug trafficking areas; and empowering consumers by raising awareness about the risks of prescription opioid misuse. Evans reported that CDC is funding an epidemiologic mixed-methods evaluation of OUD treatment in real-world outpatient settings to better understand the interaction among patients, providers, sites, and treatment type. The study's objectives are to improve treatment outcomes and to inform evidence-based decision making by policy makers, providers, and other stakeholders.

Judith Steinberg explained that HRSA supports health centers in implementing a patient-centered medical home model of care for OUD that integrates behavioral and psychosocial health interventions. The agency also supports workforce development and rural service delivery through telehealth modalities and is working to integrate treatment for OUD into primary care. She said that ongoing challenges include recruiting and retaining providers licensed to prescribe MAT; reimbursing services delivered by support providers; addressing stigma among providers and the community; and coordinating complex, timely, and comprehensive care for OUD. Steinberg said that establishing an evidence base for new models of care, such as MAT delivery in primary care, will be needed to satisfy the stringent requirements of payers. She said evidence is also needed to support the scale up of models that target vulnerable populations that need a customized care approach.

There are currently three FDA-approved medications for treating OUD: methadone, buprenorphine, and naltrexone. According to Rigo Roca, FDA, there are currently 55 active marketing applications related to these three medications, including new drug applications and abbreviated new drug applications (for generic formulations). Recent approvals include buprenorphine depot and another buprenorphine-naloxone film. He explained that they have fast-track and breakthrough therapy designations that can help to expedite regulatory approval for eligible new therapies for MAT. FDA has hosted various meetings to explore ways to expand MAT access and to support patient-focused drug development. Lastly, he noted that FDA also recently published draft guidance on the development of depot buprenorphine products and on endpoints for MAT effectiveness.

CURRENT EVIDENCE AND PRACTICE ON MEDICATION FOR TREATING OPIOID USE DISORDER

The second session surveyed the current evidence and practice on medication for treating OUD. Specifically, the session explored—for each medication—the evidence of effectiveness and evidence gaps related to use (e.g., what is known regarding dosing ranges and optimal duration of treatment); regulations, infrastructure, and care settings required for delivery; and provider and patient preferences and challenges.

Charles O'Brien, University of Pennsylvania, traced the history of opioids as pain treatment from ancient Mesopotamia to the synthesis of heroin in the 19th century to the federal policy restricting or criminalizing opioids for most of the 20th century. Widespread opioid prescribing for non-cancer pain in the 1990s catalyzed the parallel epidemic of street opioids at the core of the current crisis, he explained. Providers remain largely uneducated about addiction and opioids, he said, and he emphasized the need to distinguish between physical dependence, which is a normal physiological process, and addiction, which involves compulsive drug-seeking behavior despite harmful consequences. He also highlighted the need for education and comprehensive approaches for pain management and more extensive use of non-pharmacological pain treatments, which have no risk of addiction.

[1]The Drug Abuse Treatment Act of 2000 (DATA 2000) requires physicians to obtain a waiver to prescribe buprenorphine in office-based settings.

Methadone and buprenorphine are the two FDA-approved opioid agonist medications[2] for OUD. Methadone's effectiveness in treating OUD is indisputable, said Gavin Bart, University of Minnesota. Methadone reduces all-cause mortality, opioid-related mortality, and the risk of acquiring and transmitting HIV (Larochelle et al., 2017; MacArthur et al., 2012; Sordo et al., 2017). He explained that treatment retention improves when people receive higher doses of methadone and with structural advantages such as take-home dosing privileges and nearby treatment settings (Bart et al., 2012; Chutuape et al., 1999; Hser et al., 2011; Simpson et al., 1997; Villafranca et al., 2006). Concerns about methadone's safety persist, he added, despite clear evidence that methadone prescribed at clinics contributes minimally to overdose deaths and that the incidence of cardiac adverse events is not clinically significant (Bart et al., 2017; Johnson and Richert, 2015; Jones et al., 2016; Lofwall and Havens, 2012). Despite the wealth of evidence supporting methadone treatment, it remains stigmatized and excessively regulated; as a result, most people with OUD lack access to long-term methadone treatment (IOM, 1995).

Michelle Lofwall, University of Kentucky, explained that buprenorphine is effective in decreasing mortality (Larochelle et al., 2017; Schwartz et al., 2013). Concerns about diversion and misuse[3] underpin stringent regulatory policies—such as the buprenorphine prescribing waiver and prior authorization criteria—that reduce treatment access, despite evidence that most buprenorphine diversion is actually driven by lack of access to treatment (Lofwall et al., 2014).

Adam Bisaga, Columbia University Medical Center, addressed some common concerns about naltrexone, the only FDA-approved opioid antagonist medication.[4] Starting treatment with naltrexone is challenging, he said, because it requires a period of opioid withdrawal before initiation, unlike agonist medications. He noted that it is important to distinguish between oral naltrexone and the long-acting injectable formulation. A recent study found that treatment retention with injectable naltrexone was better than oral naltrexone (Sullivan et al., 2018). Naltrexone has similar effects on retention, cravings, and opioid use as buprenorphine, he said, with a comparable overdose risk while patients are in treatment. However, he said it is easier to discontinue treatment with naltrexone—because it does not cause dependence—with the risk of overdose increasing after treatment dropout. Naltrexone tends to be a less popular MAT option, he said, but many patients and providers are not aware of its benefits or its superior injectable formulation. He maintained that naltrexone should be seen as among the range of choices for patients, in addition to methadone and buprenorphine.

John Brooklyn, University of Vermont, described how Vermont's hub-and-spoke model integrates OUD treatment into primary care. Spokes, including all buprenorphine-waivered providers, link bi-directionally to one of six regional hubs, which are federally certified opioid treatment programs (OTPs). The model aims to prevent overdoses by providing continuous treatment to everyone with OUD in the state. He reported that as of September 2017, Vermont no longer has a waiting list, OUD treatment is available on demand at any OTP, and most of the state has access to buprenorphine treatment in an office-based setting. He reported that 1.47 percent of the entire population of the state is currently on MAT. In Vermont, the per capita rate of health care expenditures (excluding OUD treatment costs) for people on MAT has declined steadily over the past decade and the expansion of access to MAT has helped stabilize overdose rates.

Maia Szalavitz, American reporter and author, argued that "MAT" is a deeply inappropriate term because medication is the cornerstone of effective OUD care, not an optional add-on. She suggested that "counseling-assisted treatment" would be more apt. As a former patient, she said the treatment she received in methadone clinics was carceral and humiliating. Treating OUD in "ghettoized" methadone clinics is deeply problematic, she said, because it perpetuates stigma and discrimination against people who deserve equitable, respectful, evidence-based care. She said that some people want to come off methadone because the system is so horrible and they perceive it as a "chemical parole," not because of the medication itself. Stipulating that life-saving medications for OUD are contingent on conditions such as counseling, 12-step programs, or abstinence from other drugs would be unthinkable for any other chronic condition, she remarked. Two-thirds of drug courts prohibit MAT entirely and they often mandate participation in Narcotics Anonymous, which does not consider people on medication to be "clean." She added that the demeaning and hostile language used by the health care and judicial systems to describe addiction exacerbates that stigma.

Panelists discussed why treatment programs that discourage or prohibit medications are still so prevalent, given the known effectiveness of MAT. Bart said that such programs will continue to exist as long as they are funded. Several participants noted that many persons on MAT are also denied housing, prevented from participating in sober living environments, taken off medication while incarcerated, and denied other services because of their medication status. Bart emphasized the need to clarify the Americans with Disabilities Act and the Fair Housing Act as including MAT to prevent the ongoing discrimination of persons on MAT. Lofwall commented that the language around addiction must change to better align with the concept of OUD

[2]Opioid agonist medications work by activating the mu-opioid receptor in ways that yield some rewarding effects. Methadone is a full agonist that fully activates the receptor, while buprenorphine is a partial agonist that partially activates the receptor with a ceiling effect that diminishes its potential to cause rewarding effects.

[3]Lofwall defined diversion as the misappropriation of medication prescribed to somebody else, whether or not money is exchanged, and misuse as taking medication in a way other than intended.

[4]An opioid antagonist medication prevents opioids from activating the opioid receptor system, unlike methadone or buprenorphine.

with other chronic medical conditions. In the context of medication choice, Brooklyn and Szalavitz emphasized the importance of patients' preferences and shared decision making. Several participants discussed that the strong public bias toward getting off medications and tapering is largely due to the stigma of addiction and its treatment; for patients with conditions such as diabetes and HIV, the focus primarily is on staying on medications that treat the condition. Lofwall commented that the patient's insurance largely dictates the choice of MAT, while Bisaga noted that many programs only offer a single type of medication.

IMPLEMENTATION AND UPTAKE: EXPLORING OPPORTUNITIES AND BARRIERS

During the third session of the workshop, opportunities and barriers with respect to the implementation and uptake of MAT were explored. The session featured three panels that covered education and training; health care delivery, payment approaches, and economic measures; and social determinants of health. The speakers' presentations are organized here according to the panel in which they spoke, but many touched on a full range of these often interconnected barriers and opportunities.

Education and Training

The first panel focused on the opportunities and barriers related to education and training, including exploring the currently required education and training for providers and potential improvements; identifying the best practices and hurdles to achieving the required workforce to treat OUD; and examining the communication and education needs for patients, families, policy makers, law enforcement, the public, and other stakeholders.

Jeannette Tetrault, Yale University, said that they are developing a thread of addiction content throughout all medical training at the residency, advanced, and fellowship levels of the university. A component of the curriculum is explicitly designed to stop perpetuating the stigmatizing language around addiction in medical training and among faculty educators and mentors. Medical students today tend to be committed to social justice issues and eager to take on the task of ending the OUD epidemic, she said, and making education on addiction care a core requirement would bolster those efforts.

Stephen Patrick, Vanderbilt University, discussed ways to improve outcomes for pregnant women, babies, and adolescents. MAT access is substantially inadequate for vulnerable populations with OUD: only half of pregnant women and one-quarter of youths receive treatment; less than 5 percent of adolescents on Medicaid receive methadone or buprenorphine (Hadland et al., 2017, 2018; Haight et al., 2018; Short et al., 2018). He said that this gap underscores the urgent need for more pediatricians and obstetricians to become buprenorphine-waivered. He reported that both buprenorphine and methadone are recommended for OUD in pregnant women to decrease their risk of overdose and relapse and their infants will have a greater chance of going to term and having a higher birth weight. Infants have an elevated risk of neonatal abstinence syndrome if the mother receives MAT, but new models of trauma-informed, standardized, collaborative care are significantly reducing the length of stay in the hospital and are more inclusive of the mother's needs (Wachman et al., 2018). Patrick noted that the literature on long-term outcomes from neonatal abstinence syndrome is limited, but the long-term effects do not appear profound. He added that early intervention and home nursing visitation services for children born with neonatal abstinence syndrome are effective, but likely underutilized.

Eugenia Oviedo-Joekes, University of British Columbia, described the benefits of short-acting injectable medications for treating patients with the most severe OUD. She said that in addition to methadone, buprenorphine plus naloxone, and slow-release oral morphine, Health Canada offers diacetylmorphine (pharmaceutical-grade heroin) and hydromorphone (dilaudid) short-acting injectable medications as treatment options in controlled settings for people who cannot or will not stop using street drugs. She said that this is a critically important, evidence-based treatment modality for those whom the system failed—for example, people from indigenous communities disproportionately affected by OUD with a history of oppression that discourages care seeking. Offering the option of short-acting injectables engages patients in shared decision making with their provider, reduces the stigma and judgment, and "meets people where they are" to address their full spectrum of needs.

Jules Netherland, Drug Policy Alliance, situated drug use and addiction within a broader public health approach for expanding access to MAT. She called for addressing the social determinants of OUD, decriminalizing drug use, eliminating punitive policies, and integrating harm reduction services. She suggested exploring outcomes other than abstinence within this broader view, such as quality of life, family reunification, stabilization, and employment. People who use drugs should contribute meaningfully to the development of policies and provider training to represent the voices of those directly impacted, she stressed. Netherland described a host of innovative service delivery models to expand access to MAT, including office-based methadone, pharmacy-based methadone and buprenorphine, induction and maintenance in emergency departments (EDs), telemedicine, and mobile delivery. She also said education and training on MAT should be expanded beyond medical providers to individuals that work with hard-to-reach populations, such as street-based medicine, homeless service, and housing providers.

Kathleen Johnson, Advocates for Opioid Recovery, shared her experience of supporting a son with OUD to illustrate its destructive effect on the infrastructure of people's lives. People with OUD often struggle to stay afloat and on treatment in

the face of overwhelming obligations to their families, work, school, finances, and the criminal justice system. She said that broad structural changes are urgently needed so that patients, families, and communities can surmount this multigenerational, decades-long challenge. She remarked that a delicate balance needs to be struck in supporting patients' and families' decision making without overstepping the bounds.

During the panel discussion on mandating or incentivizing provider education on OUD, Tetrault suggested that institutions should be incentivized to have faculty who can model integrated addiction care and that all medical schools should have addiction fellowships. Patrick proposed that medical education at all levels and for all providers, including allied health professionals, should include addiction training and trauma-informed care. He noted that some states require continuing medical education on opioid prescribing for medical licensure, which could be a mechanism to expand provider knowledge on addiction and MAT. He added that patients' and families' experiences in the health system should be integrated into provider education to help mitigate the stigmatizing, mistaken belief that MAT is simply trading one drug for another.

Panelists discussed how to disseminate information about MAT to patients, families, and communities at large. Johnson said that information from grassroots and social media sources is often more helpful than official sources of information that are siloed and difficult to access in a crisis. Oviedo-Joekes explained that when her group publicized the results of a large clinical trial on hydromorphone, an entire team—including patients—collaborated to create a full media communication plan with a clear message that everyone would adhere to, which was vital to preventing the message from being distorted by the media. Netherland suggested partnering with advocacy organizations with experience translating technical findings into lay language for targeted dissemination. She said that crafting the product's format and delivering it in appropriate ways requires working closely with patients and families directly impacted by OUD. Patrick remarked public perception drives policy change and it is incumbent on providers and researchers to frame the narrative carefully using language that reduces stigma and is inclusive of all communities affected by the opioid epidemic since its inception decades ago. Netherland added that efforts to remedy some of the social injustices inflicted on people of color with OUD, for example, might frame the narrative with the same type of humanizing backstories afforded to white victims of the epidemic.

Health Care Delivery, Payment Approaches, and Economics Measures

The second panel explored the opportunities and barriers related to health care delivery, payment approaches, and economics measures to improve the treatment of OUD. The objectives were to discuss how health care access and delivery impact patient access to medications to treat OUD; consider regulations around hospital capacity, administrative burdens, and the tight regulation of medical products; explore the cost, reimbursement, and coverage of medications to treat OUD and discuss measures to help facilitate quality improvement and access; and examine the regulatory differences of for-profit versus nonprofit treatment providers.

Richard Frank, Harvard University, focused on economic issues in improving the treatment for OUD. He began with the demand side: 11–26 percent of people with OUD receive treatment, and among those who do, 34 percent receive MAT (Knudsen et al., 2011); around 50 percent of people are still in treatment after 1 year (Blanco et al., 2013); and people with OUD tend to wait between 4 and 7 years after developing the condition before starting treatment (Wang et al., 2005). On the supply side, he said, around 40 percent of treatment facilities offer MAT—with less than 3 percent offering all three forms (Jones et al., 2015) and less than one-quarter of publicly funded facilities offering MAT (Knudsen, 2015). Wide disparities in Medicaid coverage of OUD treatment across states have serious implications for access, because OUD disproportionately affects people with low income. He explained that MAT has traditionally been highly constrained by insurance regulations, but recent Medicaid expansions have spurred rapid growth in MAT, driven largely by office-based buprenorphine (Maclean and Saloner, 2017). Integrating MAT into general medical practices could substantially increase access, he suggested, but low reimbursement levels disincentivize providers from offering it. He advised that payment models should be better aligned with effective care models and that some of the care management burden should be shifted to non-physician providers—e.g., through bundled payments that link payment to services from outreach to retention. Frank said that the policy levers with the greatest potential payoff to expand MAT access include Medicaid expansion and design, parity implementation, and state regulation of OUD programs and licensure.

Allan Coukell, The Pew Charitable Trusts, remarked that few state-level policy makers have the holistic vision needed to address widespread shortfalls in treatment capacity. Addiction is still not commonly understood as a chronic disease and is compounded by the lingering preference for residential, abstinence-only care among many patients, families, policy makers, and payers. He explained that insurance companies often limit their coverage of MAT; thus discouraging providers while continuing to provide full coverage for non-evidence-based care. He added that administrative burdens arise from low reimbursement levels and lack of uniform prior authorization criteria across payers.

Katrina King, George Mason University, shared her experience as a patient with OUD and as the mother of a child who died by heroin overdose shortly after requesting MAT and being waitlisted. She outlined some of the obstacles that prevent

people from receiving life-saving treatment: lack of insurance coverage, expensive providers, waitlisting, stigma among providers, and the lack of peer recovery support. King has drawn on her firsthand experiences to become a community health navigator. Peer navigators have the shared lived experience to guide and mentor people with OUD who need help in staying on treatment, finding housing and employment, and accessing existing supports in the community. Peer navigation meets people where they are, she explained, and helps them to rebuild connections with their community.

Yngvild Olsen, Institutes for Behavior Resources, Inc., described an alternative payment model that mitigates reimbursement barriers by providing patient-centered opioid addiction treatment in outpatient (non-OTP) settings. The model aims to reimburse appropriately through a one-time initial payment to cover treatment initiation followed by ongoing monthly payments for medical, psychological, and social support services. She explained that some providers offer fully integrated care under one roof, while others join formal collaborative care arrangements. Providers are required to meet quality standards in providing evidence-based services and costs are controlled by eliminating unnecessary spending on ineffective treatments, she said.

During the discussion, panelists explored options for restructuring payments and setting performance measures for MAT. Coukell said that ideally, coverage would attach to the patient and not the facility, so the patient can go to any site and receive the most appropriate care. Frank contended that the performance metrics integrated into current measures used for accountable care organizations are deeply inadequate for mental health and addiction. To create better performance measures that are not as contingent on payment structures, he suggested creating targeted measures to capture access, quality, and retention. Olsen noted that current financial incentives and performance measures based on discharge metrics are not suitable for OUD or other chronic conditions treated by primary care or addiction medicine. She also warned that often bundled payments lack transparency and can incentivize the wrong practices in the absence of targeted performance measures linked to outcomes.

Social Determinants of Health and Special Populations

The third panel focused on the social determinants of health and treatment for OUD. The objectives were to explore the impact of comorbidities on treatment and how this may impact the uptake and overall effectiveness of medications to treat OUD; consider how pregnancy, age, race, gender, genetic variables, mental health, chronic pain, and other factors may influence treatment; and identify further evidence needed to better deliver culturally appropriate care and serve diverse populations.

Mishka Terplan, Virginia Commonwealth University, remarked that women are highly motivated to maximize the health and well-being of their pregnancy, including significant behavior change. Virtually all women with OUD who become pregnant will try to stop using, he said, but their addiction can make it difficult or even impossible to stop without medication to treat withdrawal symptoms. Overdose is one of the leading causes of maternal deaths in the United States and the risk of overdose increases as the postpartum period progresses (Schiff et al., 2018). He explained that the standard of care for pregnant women with OUD is a set of comprehensive collocated services that integrate medication, behavioral counseling, and prenatal care. When women with addiction are treated during pregnancy, birth outcomes are almost identical to women without addiction (Kotelchuck et al., 2017). Even though medications are known to be protective during pregnancy and postpartum, he warned that access to care is extremely limited. Most pregnant women with OUD receive no treatment at all (Terplan et al., 2015) and only half of those who are treated receive MAT (Short et al., 2018). He emphasized that among women who are treated during pregnancy, the postpartum period (the “fourth trimester”) is a critical inflection point when women can easily fall out of treatment due to gaps in insurance coverage and the siloed reproductive health care system.

Anand Kumar, University of Illinois at Chicago, described two vulnerable populations with OUD: people with psychiatric comorbidities and the elderly. He explained that a combination of biological and psychological risk factors plays a role in OUD and given the overlap in the neuronal circuitry underlying OUD and other psychiatric conditions, there is considerable comorbidity of psychiatric disorders. Common comorbidities include major depression, anxiety disorders, posttraumatic stress disorder, other substance use disorders, antisocial personality disorder, and borderline personality disorder. Comorbidities are associated with poorer outcomes in OUD, he said, with some evidence suggesting that treating comorbid conditions may improve the treatment, psychosocial, and functional outcomes of OUD. He added that a range of evidence-based, non-pharmacological psychotherapeutic approaches can also be used to help manage anxiety and depression in the context of addiction treatment. Kumar also noted that older adults present a vulnerable population with regard to opioid use, but receive comparatively little attention. Kumar reported that individuals ages 65 and older represent 25 percent of long-term users of opioids (Mojtabai, 2018), and he emphasized the need for provider education about the special biological and psychosocial vulnerabilities of this population.

Josiah Rich, Brown University, described the process of incorporating MAT into OUD treatment for incarcerated populations in Rhode Island. After implementing a universal screening program, starting everyone with OUD on treatment, and connecting people to continuation treatment upon release, the number of post-release overdose deaths dropped by 60 percent

within 1 year. He found that most people want to be treated when they have access and that people generally have a strong preference for either methadone or buprenorphine; few choose depot naltrexone. He noted that MAT is not offered in most correctional facilities and if it is, only one medication is typically offered—usually depot naltrexone, due to the stigma about agonist therapies. Investing in treatment for incarcerated populations and connecting people to maintenance treatment after release are critically important, he said, but parallel efforts need to work toward diverting people with OUD directly into treatment rather than into the criminal justice system.

Helena B. Hansen, New York University, sketched the history of racial inequalities in addiction treatment to spotlight the biases that continue to permeate U.S. drug policies. She explained that the perceived universality of the opioid crisis today is the product of the specific ethnic marketing of opioids through a separate track of legal, protected narcotics for middle-class whites as well as drug policies that favor white consumers, such as buprenorphine deregulation. During the narcotic epidemic among the black working class decades ago, racial imaging was used to justify the war on drugs, she said. This led to racially disparate law enforcement and mass incarceration, instead of public outcry and efforts to address the social determinants of drug use. The impact of the opioid crisis on whites opens a window of opportunity to address those social determinants, said Hansen. Achieving a population-level public health impact with MAT will require intervening on social structures and inequalities through structural change, she added. To help dispel the historical legacy of suspicion and distrust of health care providers and medication among low-income communities of color, she suggested packaging medication together with social services, community building, and other deliberate social technologies for fostering connections and providing assistance with basic needs. She added that educating providers on the social determinants of addiction would help work against the bias and stereotyping that abounds in clinical practice.

KNOWLEDGE GAPS, FUTURE RESEARCH, AND POTENTIAL POLICY CHANGES

The fourth session focused on knowledge gaps, future research, and next steps. As in previous sessions, speakers addressed a mix of interconnected topics, speaking both of the need to take immediate action to help those now suffering from OUD, as well as the need to advance understanding of how best to deliver and increase access to MAT.

The opioid epidemic has generated unprecedented demand for services, said Sharon Walsh, University of Kentucky, and the most impactful intervention against the rising overdose death toll is expanding treatment for OUD (Pitt et al., 2018). Of the small proportion of people with OUD who get treatment at all, the majority receives treatment that is not evidence-based and potentially harmful, she said. Many people enter prison-like, full-abstinence inpatient facilities where they painfully detoxify without medications that could alleviate their withdrawal symptoms. More affluent people may go to expensive luxury facilities, she added, but regardless of the setting, the end result is usually the same: most people will relapse and then begin the cycle anew. Walsh argued that policy must drive a paradigm shift toward quality, evidence-based, integrated care and against the abstinence-only dogma believed by many patients, communities, providers, and the justice system. She called for an immediate end to federal funding of programs that prohibit evidence-based care. Excessive regulatory barriers to MAT access also need to be lifted, she said, including insurers' fail-first policies and the requirement that both prescriber and implementer must be waivered for the new buprenorphine implant.

Gail D'Onofrio, Yale University, described the role that EDs can play in fighting the opioid crisis. EDs can identify patients, initiate treatment with buprenorphine, distribute naloxone, and link patients to treatment. Only 28 percent of opioid overdose survivors are linked to MAT (Larochelle et al., 2018) despite evidence that people given ED-initiated buprenorphine are twice as likely to be engaged in treatment after 1 month (D'Onofrio et al., 2015). To integrate research into practice, a quality framework for ED treatment of OUD was developed (Samuels et al., 2018). D'Onofrio suggested starting patients on treatment in the ED with high-dose buprenorphine that will last for a few days to sustain them until they can get into treatment, using new longer-acting buprenorphine injectables, and creating referral pathways out of the ED. D'Onofrio said that training on OUD care should be an expectation—not a request—of clinicians that is required by all health systems. The time to act is now, she urged, rather than waiting for research and knowledge gaps to be addressed.

Jonathan Watanabe, University of California, San Diego, discussed the pivotal role pharmacists can play in improving access to MAT. Evidence suggests that having pharmacists directly interface with clinicians to inform them about MAT has the potential to increase access. He suggested that analytics could accelerate efforts to reach more patients by monitoring opioid use and managing the availability of MAT for facilities. Pharmacies and community care clinics can serve as access points and mechanisms for reaching patients in areas hard hit by OUD but underserved by health care systems, he explained. Watanabe reported that there is interest among the pharmacy community about the possibility of allowing pharmacists to obtain waivers to administer buprenorphine, using the rationale that OUD is a public health threat.

Jessica Hulsey Nickel, founder of the Addiction Policy Forum, an OUD patient advocacy group, said that bridging the gap among clinicians, scientists, and the patient community will help to reduce the isolation and stigma that patients and families experience. She shared stories of patients and families to humanize the devastating consequences of the epidemic. Nickel

noted that the current treatment system is built for adults, even though OUD often begins to develop in adolescence. She said that "catch and release" practices in hospitals are far too common: the same person is revived from overdoses on multiple occasions without ever being guided into treatment for OUD. Patients seeking MAT are regularly refused treatment based on insurance companies' fail-first policies and many go on to overdose shortly after. Patients and their families face pervasive stigma about addiction as a decision, not a disease, and must navigate a "troubling constellation of myths and misinformation" about OUD to find effective, evidence-based care for their loved ones. Her organization is working to build awareness and fight against entrenched misconceptions.

During the discussion on research needs, Watanabe suggested more operational research to address logistical and reimbursement challenges related to addiction care. D'Onofrio called for research on starting and retaining patients in treatment, high-risk behaviors in adolescents and how to intervene, harm reduction, reaching young adolescents, and the integration of psychosocial therapies with MAT. Walsh remarked that better medications to treat OUD are needed, but if structural barriers prevent patients from accessing them, then the pharmaceutical industry will not invest in developing them. She added that evidence should be used to eliminate the policies and practices that do *not* work—for example, detoxification without medication and barriers to buprenorphine delivery. Nickel suggested using multidisciplinary approaches to investigate various combinations of medications and psychosocial interventions to treat OUD of different severity levels.

In closing the workshop, Alan Leshner, chair of the Committee on Medication-Assisted Treatment for Opioid Use Disorder, thanked all of the speakers, noting that the presentations and discussions generated a great deal of thought and discussion and will be a valuable supplement to the literature reviews. He reminded attendees that the committee will draft a Consensus Study Report that will undergo the National Academies peer-review process and be released in spring 2019.♦♦♦

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[5] This reference was updated since the release of the publication.

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Urine Drug Testing

Recommendation #10 from the CDC *Guideline for Prescribing Opioids for Chronic Pain* states, "When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs."

When to conduct urine drug testing:

All patients on long-term opioid therapy should have periodic urine drug tests (UDT). Medical experts agree that an annual UDT for all patients should be standard practice[i]. Subsequent UDTs should be determined on an individual patient basis, at the discretion of the clinician. Before ordering a UDT, have a plan for responding to unexpected results.

tips

WHAT TO DISCUSS WITH PATIENTS BEFORE ORDERING AND CONDUCTING A URINE TEST:

Establish provider/patient trust

Requiring a UDT does not imply a lack of trust on the part of the provider; it is part of a standardized set of safety measures offered to all patients taking opioids.

Discuss the purpose of UDTs

What drugs the test will cover, and the expected results (e.g., presence of prescribed medication and absence of other drugs, including illicit drugs, not reported by the patient).

Go over the potential cost

If the UDT is not covered by insurance.

Review dosage

Review the time and dose of the opioids most recently consumed by the patient.

Discuss any prescribed or unprescribed drugs

Discuss any other prescribed or unprescribed drugs the patient has taken; unprescribed drugs may include marijuana or other illicit drugs.

Ask the patient what UDT results he/she expects

To aid in eliciting information on other drugs taken as well as to assess his/her understanding of test result interpretation.

Establish the expectation of random repeat testing

Establish the expectation of random repeat testing depending on treatment agreement and monitoring approach.

Review

Review actions that may be taken based on the results of the test.

[i] *Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR 2016.*

If unexpected results occur when ordering a UDT, remember that the focus is to improve patient safety. Have a plan in place for communicating results and practice the difficult conversations you may have with your patients.

tips TALKING WITH PATIENTS ABOUT URINE DRUG TESTING RESULTS:

- Always keep the focus on the patient's well-being and safety.
- Do not jump to conclusions about unexpected results; have a candid conversation with the patient about possible explanations.
- Do not dismiss patients from care based on UDT results.
- Consider using the CDC mobile app to practice the types of conversations you may encounter with patients.

Actions to take post-urine drug testing:

- Discuss unexpected results with the local laboratory or toxicologist if assistance is needed with interpretation.
- Inform the patient of the test results.
- Take time to discuss unexpected results with the patient and refer to pre-UDT information the patient may have shared with you.
- Review the treatment agreement and focus conversations around patient safety.
- Determine if frequency and intensity of monitoring should be increased and keep the patient informed.

Types of urine drug tests:

There are two main types of UDTs— immunoassay drug testing conducted at a laboratory or at the point of care in a provider's office, and laboratory-based gas or liquid chromatography/mass spectrometry. See the chart below for a description of the main differences in these two types of tests.

IMMUNOASSAY	GAS CHROMATOGRAPHY, MASS SPECTROMETRY
Less expensive, fast, easy to use	More expensive, labor intensive
Most frequently used technique in all settings, including hospital labs	Requires advanced laboratory services.
Used commonly as screening test.	Used primarily to confirm positive immunoassay result.
Engineered antibodies bind to drug metabolites	Measures drugs and drug metabolites directly.
Qualitative testing-- positive or negative	Quantitative testing
Screens for presence of drugs or a panel of drugs: amphetamine, marijuana, PCP, cocaine, natural opiates (morphine/ codeine/thebaine but without differentiation). Heroin is metabolized to morphine and can therefore be detected; a separate screening assay specific to heroin is also available.	Identifies specific drugs and their metabolites
Does not differentiate various natural opiates	Differentiates all opioids
Typically misses semisynthetic (e.g. hydrocodone and oxycodone) and synthetic opioids (e.g. fentanyl and tramadol). Assays specific for these drugs must be requested.	More accurate for semisynthetic and synthetic opioids--methadone, propoxyphene, fentanyl, meperidine, hydrocodone, oxycodone, hydromorphone, oxymorphone, buprenorphine, heroin
Often has high cut- off levels, giving false negative results	Very sensitive, detects low levels of drug, minimizes false negatives
Will show false positives: poppy seeds, quinolone antibiotics, over-the-counter medications	Very specific, less cross-reactivity, minimizes false positives

Source: Adapted from "Urine Drug Testing in the Management of Chronic Pain," at https://www.drugabuse.gov/sites/default/files/files/UrineDrugTesting.pdf

To learn more, visit: www.cdc.gov/drugoverdose/prescribing/qi-cc.html

CDC's Efforts to Prevent Opioid Overdoses
AND OTHER OPIOID-RELATED HARMS

CDC's work focuses on five areas:

Conducting Surveillance & Research

Building State, Local, & Tribal Capacity

Supporting Providers, Health Systems, & Payers

Partnering with Public Safety

Empowering Consumers to Make Safe Choices

Conduct Surveillance and Research

Timely, high-quality data help public health officials and other decision-makers understand the extent of the problem, focus resources where they are needed most, and evaluate the success of prevention efforts. Recognizing the importance of data, CDC is helping states track the opioid overdose epidemic and better focus their prevention activities. In addition, CDC funds research to better understand the epidemic and identify effective strategies to prevent it.

Build State, Local, and Tribal Capacity

States, local communities, and tribes play an important role in preventing opioid overdoses and related harms. They run prescription drug monitoring programs, regulate controlled substances, license healthcare providers, respond to drug overdose outbreaks, and run large public insurance programs such as Medicaid and Workers' Compensation. CDC is nationally recognized for its work with health departments and community-based organizations. The agency has a long track record of funding efforts to improve data collection and implementing evidence-based prevention strategies.

Support Providers, Health Systems, and Payers

Providers and the health systems they work in are crucial in promoting safer and more effective opioid prescribing for pain management. Use of the CDC Guideline for Prescribing Opioids for Chronic Pain by providers and health systems can improve the way that opioids are prescribed. In addition, health systems can implement quality improvement measures informed by the guideline to track their efforts and integrate these measures into their electronic health records. Private and public insurers and pharmacy benefit plan managers can foster the implementation of CDC's guideline through improvements in coverage, removal of barriers, and drug utilization review.

Partner with Public Safety

In recent years, the opioid overdose epidemic has worsened with a rise in the use of illicit opioids. Of particular concern is illicitly manufactured fentanyl, which is 50–100 times more potent than morphine. CDC has forged new partnerships with law enforcement to address the growing illicit opioid problem. The agency has partnered in innovative ways with public safety and is a leader in prevention strategies in high intensity drug trafficking areas. Greater communication and collaboration between public health and law enforcement can improve data sharing, surveillance, and the targeting of interventions.

First responders—including police, fire, and paramedics—are on the frontlines of the epidemic. They are often in a position to save lives with timely administration of naloxone.

Empower Consumers to Make Safe Choices

One of CDC's priorities is raising awareness about the risks of prescription opioid misuse with consumers. To accomplish this, CDC launched the Rx Awareness communication campaign that features testimonials from people recovering from opioid use disorder and people who have lost loved ones to opioid overdose. The goal of the campaign is to educate consumers about the risks of prescription opioids and the importance of discussing safer and more effective pain management with their healthcare providers. CDC is also promoting awareness of risks associated with non-medical use of opioids, factors that increase risks (such as fentanyl in the local drug supply), and approaches to reduce risks.

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

What You Need to Know About Treatment and Recovery

There is hope. Recovery is possible.

Addiction Is A Disease

Opioids are highly addictive, and they change how the brain works. Anyone can become addicted, even when opioids are prescribed by a doctor and taken as directed. In fact, millions of people in the United States suffer from opioid addiction.

Signs of Opioid Addiction

A major warning sign of addiction is if a person keeps using opioids even though taking them has caused problems—like trouble keeping a job, relationship turmoil, or run-ins with law enforcement. Other signs can include:[1]

Opioid Use Disorder

Sometimes referred to as "**opioid addiction,**" opioid use disorder is a chronic and relapsing disease that affects the body and brain. It can cause difficulties with tasks at work, school, or home, and can affect someone's ability to maintain healthy relationships. It can even lead to overdose and death.

- **Trying to stop or cut down on drug use, but not being able to.**
- **Taking one drug to get over the effects of another.**
- **Stealing drugs or money to pay for drugs.**
- **Using drugs because of being angry or upset with other people.**
- **Being scared at the thought of running out of drugs.**
- **Overdosing on drugs.**

[1] findtreatment.gov/content /understanding-addiction/addiction-can-affect-anyone

To learn more about opioid misuse, go to **cdc.gov/RxAwareness**.

Recovery Is Possible

Recovery does not happen overnight. Asking for help from family, friends, co-workers, and others can make a big difference. Tell them your reasons for quitting and ask them to check in with you about how things are going. If you know or suspect someone is struggling, ask if you can help.

Treatment Can Help

Treatment can help people get their lives back before it is too late. No single treatment method is right for everyone, but research shows that combining behavioral therapy with medication is the most effective approach for overcoming opioid addiction.

Addiction is a disease that for many involves long-term follow-up and repeated care to be effective and prevent relapse. **When people make a recovery plan that includes medication for opioid use disorder, their chances of success increase.** Medications can help normalize brain chemistry, relieve cravings, and in some cases prevent withdrawal symptoms.

Medication-Assisted Treatment Options

Talk with your doctor to find out what types of medication are available in your area and what options are best for you. Be sure to ask about the risk of relapse and overdose.

Methadone
• Available as daily liquid • Can only be used in a certified opioid treatment program setting

Buprenorphine
• Available as dissolving tablet, cheek film, or 6-month implant under the skin • Can be prescribed by a doctor for use outside of a clinic

Naltrexone
• Can be prescribed by any healthcare provider who can legally prescribe medication • Only used for people who have not used opioids for at least 7–10 days

Find Treatment Services

Use these resources to find services that fit your needs:

Mental Health and Addiction Insurance Help: **hhs.gov/programs/topic-sites/mental-health-parity/mental-health-and-addiction-insurance-help/index.html**

Health Center Locator: **findahealthcenter.hrsa.gov**

Behavioral Health Treatment Services Locator: **findtreatment.samhsa.gov**

Opioid Treatment Program Directory by State: **dpt2.samhsa.gov/treatment/directory.aspx**

Additional resources to access help:

- **Medication-Assisted Treatment (MAT)**
- **Decisions in Recovery: Treatment for Opioid Use Disorder**
- **Facing Addiction in America | The Surgeon General's Report on Alcohol, Drugs, and Health**