Clinical Drug Testing in Primary Care Part 2

Chapter 4—Drug Testing in Primary Care

In This Chapter

Uses of Drug Testing in Primary Care

Primary care providers order a wide array of laboratory tests as part of routine physicals and to determine the cause of symptoms, adjust medication dosages, monitor treatment effectiveness, and diagnose. Drug tests can be ordered and used for these same reasons.

Discussing substance use with patients can be time-consuming and may upset some patients. However, if a drug test is indicated, talking with patients before, after, and even if drug testing is refused can yield information that may improve many aspects of primary care. Some examples of when the use of drug testing or discussing substance use could improve patient care include:

- Evaluating unexplained symptoms or unexpected responses to treatment and identifying substance use that has contributed to, caused, or is complicating the patient's treatment;
- Evaluating patients in psychiatric care for substance abuse issues, or before prescribing psychoactive medications;
- Identifying potential substance use problems in women who are pregnant, or planning on becoming pregnant, and identifying at-risk neonates;
- Identifying patients with possible substance abuse issues;
- Monitoring patients in substance abuse treatment: to assess the efficacy of the treatment plan and the level of care, to monitor abstinence before administering medications to treat substance use disorders (SUDs), and to help identify a relapse to substance use;
- Ensuring patient safety prior to surgery or other invasive procedures to prevent medication interactions;
- Managing patients prescribed opioids for chronic pain control; and
- Monitoring potentially addictive prescription use (e.g., sedatives, tranquilizers, medications to treat attention-deficit/hyperactivity disorder [ADHD]).

Monitoring Prescription Medication Use

Drug testing is useful for monitoring patient treatment compliance with prescribed medications that have addictive properties (e.g., opioid pain medication, sedatives, ADHD medication). Test results can reveal whether patients have recently taken their prescribed medication and if non-prescribed or illicit drugs have been used. Drug testing can help practitioners identify and reduce diversion of scheduled drugs by patients.

Management of Chronic Pain With Opioids

Primary care practitioners often provide medical management for patients taking opioids for chronic pain. Long-term pain treatment with opioids requires monitoring for continuing effectiveness for pain relief and the potential for misuse, addiction, or diversion. Current clinical guidelines recommend the use of drug tests for pain management with opioids to help guide decisions about prescribing scheduled medications, revising treatment regimens, and when to initiate or refer for substance abuse treatment (Chou et al., 2009; Fishman, 2007).

Gourlay, Caplan, and Heit (2010) suggest that drug testing may be useful for:

- New patients as part of regular care to indentify the use of illicit or nonprescribed drugs;
- Patients being prescribed a controlled substance;
- Patients who present with a condition that warrants a prescription for a controlled substance and who resist a full evaluation or who request a specific medication with addictive potential;
- Patients with aberrant behavior (e.g., patients who consistently want appointments toward the end of office hours, arrive after office hours, insist on being seen immediately, repeatedly report losing prescriptions or medications, are reluctant to change medication, do not adhere to the treatment plan);
- Patients who are suspected of diversion;
- Patients who need advocacy to verify their abstinence;
- Patients in recovery from SUDs; and
- Patients who need a change in their treatment.

Katz and colleagues (2003) conducted a 3-year study on behavioral monitoring and urine drug testing in patients receiving long-term opioid therapy for pain. Their findings suggest that random drug testing of all patients receiving opioids for pain may be warranted. The researchers found that urine drug testing was much more effective than behavioral monitoring alone in identifying patients who were taking drugs other than the prescribed opioid. For example, 72 percent of patients with a positive test result did not have any behavioral indicators considered useful for screening.

Evaluation of Unexplained Symptoms or Unexpected Responses to Treatment

The results of drug tests can clarify situations in which substance use contributes to, causes, or complicates diagnosis or treatment, but the substance use is not apparent to the clinician. Patients may not disclose:

- All the medications prescribed by other providers or over-the-counter (OTC) medications and herbal products;
- That they take medications prescribed for other people;
- Use of illicit drugs or how much alcohol they consume; or
- If they have stopped taking their medications.

Following are some clinical examples of when or where drug testing might explain the cause of symptoms or unexpected response to treatment:

- A man whose hypertension remains uncontrolled, despite adhering to a low-salt diet and several antihypertensive medication changes, who does not inform the clinician that he drinks more than four drinks almost every evening and more on weekends.
- A college student who complains of heart palpitations, but does not mention using her roommate's medication for ADHD to help her study.
- An elderly woman who is increasingly confused and somnolent and has a normal physical, tests, and laboratory results, but does not state that she self-medicates with her friend's prescribed benzodiazepines to help her "nerves."
- A patient with pancreatitis who repeatedly denies alcohol use and is negative for any other causes.

In clinical situations, such as these and others, practitioners can order drug tests and use the results to gain a better understanding of the true clinical picture, determine the diagnosis, talk to the patient, and then work more effectively with the patient.

Patient Safety

In some cases, ensuring patient safety is the primary reason for testing in clinical situations. For example:

- **Preoperative or preprocedure evaluations**. Primary care providers often do evaluations for their patients prior to planned surgery or other invasive procedures. Drug tests may identify medication or illicit drug use not disclosed during the practitioner–patient interview. Drug testing can be used if the practitioner suspects that the patient is using drugs, or if the patient has a history of drug use. The primary care physician can alert the anesthesiologists or radiologists to the possible presence of substances that could cause adverse drug reactions, interfere with anesthesia, prevent possible cardiac complications or respiratory depression, prevent the patient from experiencing withdrawal if hospitalized, or poor pain management if the patient has been taking high doses of opioids and has developed tolerance.
- **Preventing toxic drug interactions.** Drug testing may reveal a patient's use of multiple substances, both legal (prescribed and OTC medications) and illicit drugs. A practitioner needs this information before prescribing a new medication or starting pharmacotherapy for SUDs, psychiatric conditions, and other health problems. For example, a toxic interaction can occur if a patient uses other central nervous system depressants while taking buprenorphine or methadone.

Pregnancy

Drug and alcohol testing of women who are pregnant or who want to become pregnant is an opportunity to prevent damage to the woman and the fetus. During preconception counseling, women should be advised about the risks of alcohol, tobacco, and drug use to the fetus. Screening for substance use should be done so that the patient can be assessed and referred to treatment before becoming pregnant. SUD screening and assessment of a pregnant woman can identify an SUD early enough for intervention and for preventing, minimizing, or at the very least preparing for serious problems for the fetus or neonate. Pregnant women should be strongly urged to abstain from alcohol and drugs, and, if necessary, referred to treatment as soon as possible. Drug testing can be used to monitor abstinence.

A difficult dilemma is created by State laws that require the reporting of nonmedical use of controlled substances by a pregnant woman or that require drug testing after delivery if illicit drug use is suspected. These laws can have the unintended effect

of women not seeking prenatal care. Drug testing during pregnancy, or postnatally, can have severe consequences. In many States, pregnant and parenting women can be reported to child protective services, even though the courts have struck down criminal charges against women who are pregnant and use drugs. Women have the right to refuse drug testing (American College of Obstetricians and Gynecologists, 2008); however, if drug abuse is suspected that is contributing to child abuse, reporting to child protective services is necessary.

Psychiatric Care

Drug testing is uncommon for patients who are primarily being treated for mental disorders, but should be considered when assessing a patient presenting with mood or behavior changes (Black & Andreasen, 2011). Drug tests could be used with patients with possible mental disorders to aid in diagnosis, help determine whether the psychiatric symptoms are substance use or withdrawal related, or to identify a co-occurring SUD.

Controlled substances are prescribed for some psychiatric conditions (e.g., benzodiazepines for chronic anxiety disorder or stimulants for ADHD). Drug test monitoring for adherence to controlled medications may be indicated for some patients.

Monitoring Office-Based Pharmacotherapy for Opioid Use Disorders

The Drug Addiction Treatment Act of 2000 (DATA 2000) permits office-based substance abuse treatment by allowing certified physicians to prescribe Schedule III, IV, and V medications to treat opioid dependence. To prescribe buprenorphine, a Schedule III opioid medication, physicians must qualify for a DATA 2000 waiver. Physicians providing office-based pharmacotherapy use drug testing to monitor compliance with pharmacotherapy and abstinence from illicit opioids. For more information, visit http://buprenorphine.samhsa.gov/index.html and see Treatment Improvement Protocol (TIP) 40: *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* (Center for Substance Abuse Treatment [CSAT], 2004).

Detection of Substance Use Disorders

Many patients seeing primary care providers have an undiagnosed SUD and providers can play important, preventive roles in detecting and addressing SUDs in the primary care setting. Drug testing can aid the provider in identifying those patients using illicit substances and screen them further for a possible SUD. It must be noted that a positive drug screen is not diagnostic in itself of an SUD.

The practitioner can find clues for a possible SUD in a patient's laboratory findings, physical examination, and medical history. For example, liver enzyme abnormalities may suggest current or past alcohol misuse or dependence, and hepatitis B and C antibodies can suggest current or past drug use. A physical examination may reveal track marks or abscesses, or a patient may have a history of medical conditions that suggests an SUD (e.g., cirrhosis, pancreatitis). Other physical signs include frequent falls or injuries, bruises the patient cannot explain, physical complaints without corresponding physical findings, deterioration in personal hygiene, and disheveled appearance.

Physical signs of SUDs may not appear until late in the progression of the disorder. Nonphysical or behavioral signs could include:

- Reports of marital, academic, or employment problems;
- Chaotic lifestyle;
- Deterioration in grooming or hygiene;
- Unusual mood swings or outbursts;
- Money or other valuable items missing from the home;

- Requests for specific potentially addictive medications; and
- Frequent reports of losing prescriptions for potentially addictive medications.

Initial Assessment of a Person With a Suspected SUD

A positive drug test does not necessarily indicate a diagnosis of an SUD. The drug use could be sporadic and not meet the diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (American Psychiatric Association, 2000). These patients will need screening and assessment. When informing a patient about the test results of an initial assessment, the practitioner can:

- Inform the patient about the health and medical consequences (Fleming, 1995). Once screening results are explained, describe the health risks and medical consequences of use of the substance in question. For some (e.g., people with chronic hepatitis) any consumption of a substance, such as ethanol, may be unsafe. Likewise, the use of stimulants, such as cocaine and amphetamines, could have disastrous consequences for a patient with compromised cardiac function or hypertension. Women who are pregnant or who want to become pregnant should be told of the dangers an SUD poses to the fetus and the mother, receive further assessment, or be referred to SUD treatment.
- Pay careful attention to semantics. Avoid pejorative labels of "alcoholic" or "addict." Use neutral, nonstigmatizing language (e.g., "people with substance use problems"). Do not use humiliating or confrontational approaches to try to force the patient to agree to treatment.
- Recognize that a positive test result may trigger patient resistance or feelings of guilt, shame, or anger. Avoid arguing with the patient. Negative reactions can often be countered by focusing on the relationship between the original health complaint and the patient's use of drugs or alcohol.
- Demonstrate an understanding and acceptance of the patient and communicate that the clinician will help the client help himself or herself.
- Address goals and strategies for change. Assess the patient's readiness for change. Help the client clarify the nature of his or her difficulties. Express empathy and a willingness to listen to the client. Use motivational counseling approaches to encourage further screening or assessment or treatment options. Foster hope for positive change. Resources for more information about motivational approaches are in Exhibit 4-1.

A positive test result for illicit drugs or nonprescribed licit medications does not necessarily mean that the patient has an SUD; it means that the SUD may exist and the patient needs further screening to rule out an SUD or determine whether an SUD assessment is needed. The practitioner can do brief office-based screening, using the test result to start a discussion. The practitioner can also use a screening instrument; the simplest and quickest screening instrument is CAGE-AID (Exhibit 4-2). CAGE-AID is a tool that has been tested with primary care patients (Brown & Rounds, 1995).

Exhibit 4-1. Motivational Interviewing Resources

- TIP 35: *Enhancing Motivation for Change in Substance Abuse Treatment* (CSAT, 1999b)
- *KAP Keys for Clinicians Based on TIP 35* (CSAT, 2001a)
- *Quick Guide for Clinicians Based on TIP 35* (CSAT, 2001b)
- *Motivational Interviewing: Preparing People for Change* (Miller & Rollnick, 2002)
- The Motivational Interviewing Page (http://www.motivationalinterview.org)
- *Helping Patients Who Drink Too Much: A Clinician's Guide, Updated 2005 Edition* (National Institute on Alcohol Abuse and Alcoholism, 2007)

Exhibit 4-2. The CAGE-AID Questions

1. Have you felt you ought to **C**ut down on your drinking or drug use?
2. Have people **A**nnoyed you by criticizing your drinking or drug use?
3. Have you felt bad or **G**uilty about your drinking or drug use?
4. Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (**E**ye-opener)?

The National Institute of Drug Abuse's (NIDA's) NIDAMED provides resources for health professionals and is available at http://www.nida.nih.gov/nidamed/screening/.

The NIDAMED Web site includes a number of resources, such as:

- NIDA's Clinician's Screening Tool, NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NMASSIST), is available online and in hard copy.
- Resource Guide: Screening for Drug Use in General Medical Settings provides information on using the 5As–Ask, Advise, Assess, Assist, and Arrange.

NMASSIST is a well-validated tool in general medical settings. The empirical evidence is good for screening and brief intervention for alcohol use disorders in a primary care setting, but it is more limited for the treatment of drug use disorders, which might require a more intensive care setting.

Several screening and assessment tools are listed in Appendix C—Screening and Assessment Instruments in TIP 24: *A Guide to Substance Abuse Services for Primary Care Clinicians* (CSAT, 1997).

When screening or a brief assessment indicates a problem with substance use, the practitioner may want to try brief office-based interventions. A brief intervention is a pretreatment tool or prevention technique that involves office-based, practitioner-patient contacts of 10–15 minutes for a limited number of sessions. The number and frequency of sessions depend on the severity of the problem and the patient's response. A brief intervention can be useful before or after an indepth assessment and both during and after specialized treatment as part of followup and relapse prevention. Exhibit 4-3 lists basic elements of brief interventions using FRAMES. More indepth information can be found in TIP 34: *Brief Interventions and Brief Therapies for Substance Abuse* (CSAT, 1999a); TIP 24: *A Guide to Substance Abuse Services for Primary Care Clinicians* (CSAT, 1997); *Brief Intervention for Hazardous and Harmful Drinking: A Manual for Use in Primary Care* (Babor & Higgins-Biddle, 2001); and at the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Web site on screening, brief intervention, and referral to treatment http://www.samhsa.gov/prevention/SBIRT/index.aspx.

Exhibit 4-3. Brief Intervention Elements: FRAMES

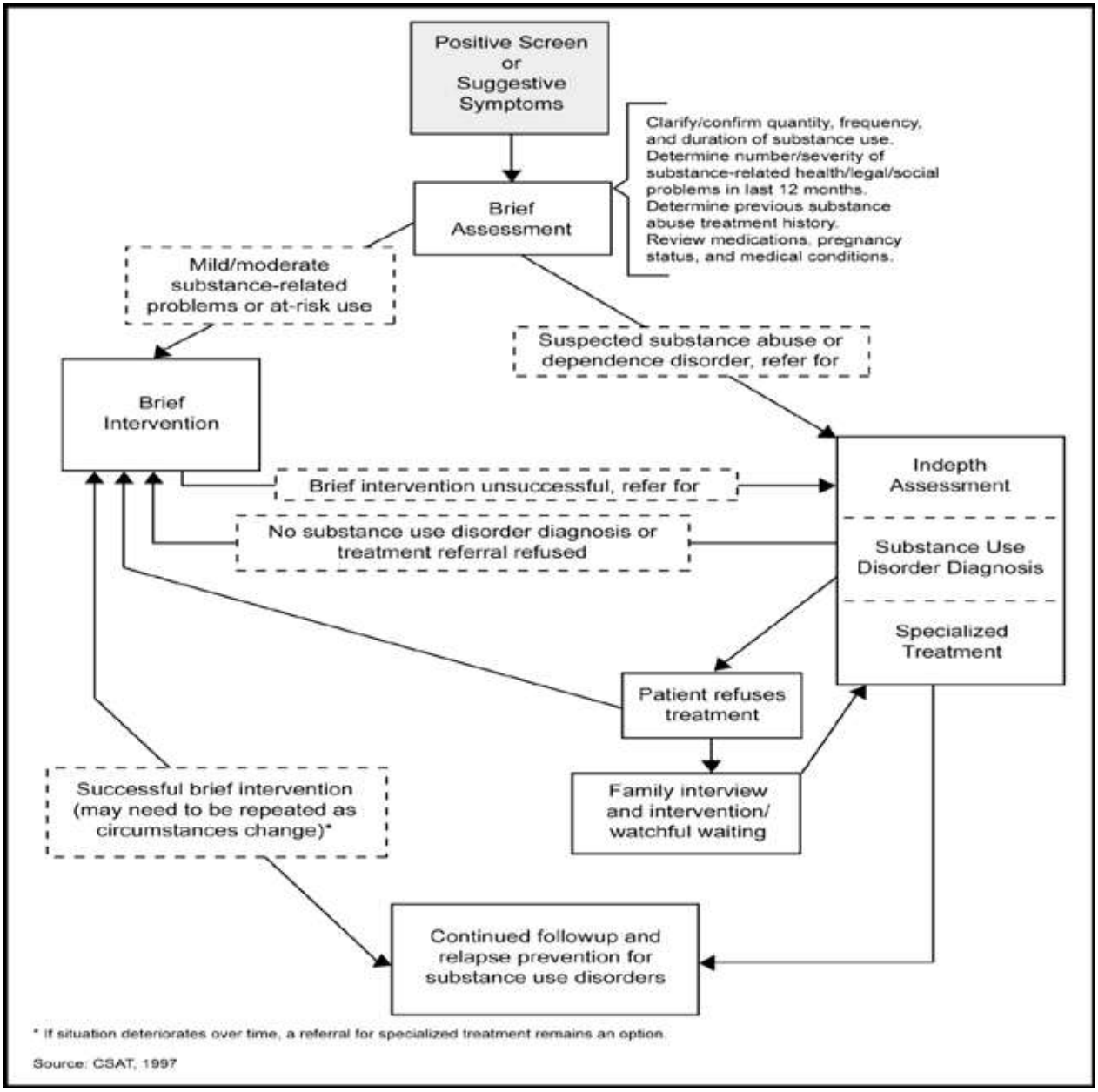
Feedback—The practitioner gives patients personalized feedback relevant to their individual situation.
Responsibility—The practitioner lets patients know that they are ultimately responsible for their recovery.
Advice—Studies have proved that even brief sessions providing information or advice about substance use can lead to behavior changes (Rollnick, Heather, & Bell, 1992).
Menu—Giving patients a menu of strategies (as appropriate to the treatment situation) adds to the sense of responsibility patients feel.
Empathy—An empathetic approach to treatment has been positively linked to positive treatment outcomes.
Self-Efficacy—The feeling of self-efficacy (e.g., I can change) is critical to promoting behavioral changes in patients. Patients' belief that they are capable of changing their behavior can help them through challenging parts of recovery.

SOURCE: Miller & Sanchez (1994)

If a practitioner suspects an SUD, he or she can refer the patient to appropriate psychosocial or medication-assisted treatment services. Often, making a telephone call to a treatment facility while the patient is in the office is the best way to get a patient to treatment. Substance abuse treatment providers will do a thorough assessment and recommend the least intensive environment that is safe and effective for the patient.

The practitioner should follow the patient's progress in treatment and request evidence of the patient's adherence to prescribed psychosocial services. Brief interventions can be successful. The patient could also have drug tests during subsequent visits to assess progress. Exhibit 4-4 provides a flowchart of the screening, assessment, brief intervention, and referral processes in primary care settings.

Exhibit 4-4. Patient Flow Through Screening and Referral in Primary Care



For more information, refer to the following publications:

- TIP 24: *A Guide to Substance Abuse Services for Primary Care Clinicians* (CSAT, 1997)
- TIP 40: *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* (CSAT, 2004)
- TIP 49: *Incorporating Alcohol Pharmacotherapies Into Medical Practice* (CSAT, 2009)
- *Screening for Drug Use in General Medical Settings, Quick Reference Guide* (NIDA, 2009)
- *Helping Patients Who Drink Too Much: A Clinician's Guide* (National Institute on Alcohol Abuse and Alcoholism, 2007)

Talking With Patients About Drug Testing

Prior to testing, important tasks for the practitioner are to explain to patients: (1) the reasons for performing drug testing, (2) use of the test results, and (3) the practitioner's duty to maintain confidentiality. It should also be explained to the patient that the drug tests and the results will become part of the patient's record. Establishing a trusting relationship in which patients feel comfortable about confiding substance use helps address any questions or negative reactions to testing or test results. If the patient has language, hearing, or vision-related challenges, accommodations may need to be made with the use of a translator or assist technologies. Key practitioner actions that contribute to such a relationship include:

- Communicating openly;
- Having an understanding attitude;
- Listening actively;
- Treating the patient with dignity and respect;
- Reassuring the patient regarding confidentiality of medical records;
- Having a straightforward, but nonjudgmental attitude; and
- Using a matter-of-fact, nonconfrontational approach in explaining the reasons for drug testing and any subsequent treatment.

Explicit consent for drug testing is not required in primary care settings. However, there are reasons why practitioners should inform patients before drug testing:

- **The practitioner–patient relationship**. Although patients may assume they will be tested for cholesterol or glucose levels, most do not expect to be tested for drug use. Patients confronted with results of tests that they did not realize were being performed may feel betrayed by the practitioner, possibly eliminating the chance for discussion about substance use problems and harming the practitioner–patient relationship.
- **Privacy**. If the practitioner orders a test and the cost is submitted to the insurance company, the patient's health insurance company will know about it. Patients should have the choice of deciding whether they are willing to have their insurance carrier learn this information.
- **Reimbursement**. Patients' third-party payers may not cover drug tests. If insurance companies do not pay for the test, patients should decide whether they are willing to self-pay; this decision should be made before the test is done. The patient may want to pay out of pocket to keep the drug test out of his or her insurance record.

Before testing, the practitioner needs to emphasize to patients the importance of revealing all prescription and nonprescription drugs (including OTC medications and herbal preparations) they are taking. Patients may not realize that OTC or herbal products can affect drug test results.

Even if a patient refuses to consent to a drug test, the conversation between the practitioner and patient may facilitate a discussion about possible substance use problems. The practitioner could begin by asking why the patient does not want to have a drug test, or agree to re-visit the issue during another visit. A patient may be willing to examine his or her behavior after refusing the test.

Discussing drug testing results can be difficult. Patients need clear and thoughtful explanations of the test results and the terms positive, negative, adulterated, dilute, or substituted. They need to understand why the test was positive or negative and what that means for the patient and any treatment. All results should be presented in a straightforward, nonjudgmental manner using terms the patient understands. Effective communication is essential for the practitioner–patient relationship to be successful in these circumstances.

Cultural Competency and Diversity

The ease or difficulty in establishing and maintaining a therapeutic alliance is affected by many factors, including the amount of time the practitioner can spend with the patient, the backgrounds of both the practitioner and the patient, the patient's ability to speak English, and acculturation levels (if the patient is from another country). Drug testing with some patients from diverse groups can be challenging due to their cultural beliefs, history, and heritage. Some patients may distrust the medical profession because of past abuses by the medical community. They might feel additional shame about SUDs because of the strong stigma in their community, they might fear disclosure to law enforcement, or they might possess a different idea of what constitutes normal drinking versus problematic drinking.

Some approaches to help improve communication in these circumstances include:

- Providing an explanation of the practitioner's perceptions of the problem and listening, with sympathy and understanding, to the patient's perception of the problem.
- Acknowledging and discussing the differences and similarities in beliefs about treatment.
- Recommending treatment and then negotiating a treatment agreement (Berlin & Fowkes, 1983).

Following are some ideas for the practitioner to consider when treating patients from diverse backgrounds:

- Culture is important in every patient's identity.
- Communication of cultural understanding and respect is essential for establishing rapport.
- Culture-related stresses and tensions can induce illness.
- Culture-related behaviors or beliefs (e.g., religion, family structure and influence, health practices, traditional health beliefs) affect patients' acceptance of and compliance with prescribed therapy.
- Nonverbal and verbal communication may differ from culture to culture.
- Customs and attitudes surrounding SUDs may differ from the accepted medical definition.
- Awareness of prevailing cross-cultural tensions and psychosocial issues may help the practitioner understand patients from that culture (Bobo, Womeodu, & Knox, 1991).

Intercultural skills need to be as specific as possible for each culture. For example, the practitioner should:

- Attempt to understand how the patient's background and culture can affect treatment.
- Elicit the patient's understanding of drug testing.
- Negotiate a culturally relevant care plan with the patient as partner.
- Interpret verbal and nonverbal behaviors in a culturally relevant manner.
- Acknowledge the patient's role as an active participant in his or her own care (Bobo et al., 1991).

Monitoring Patients

Patients With an SUD

If the practitioner is providing substance abuse treatment, drug testing can:

- Objectively monitor abstinence from drugs or alcohol;
- Monitor response to treatment;
- Corroborate self-reports;
- Help address denials of substance use; and
- Identify relapse to substance use.

For example, an increasing number of physicians provide medications for alcohol use disorders (e.g., disulfiram, naltrexone). Drug testing can be used to help monitor patients' use of drugs, if necessary, and is needed before starting naltrexone. The patient and practitioner need to negotiate a plan of action to address the patient's substance use and monitor progress. Any medical problem other than substance use (e.g., hypertension) should also be monitored, as should any abnormal biological markers (e.g., elevated gamma-glutamyl transpeptidase levels in patients who abuse alcohol).

A practitioner using drug tests may seem intrusive to some patients, whereas other patients welcome the discipline imposed. The practitioner and patient should negotiate the use of any form of objective monitoring beyond self-reports of substance use. Biological monitoring should be viewed as an informative measure, not cause for punitive action against the patient. Repeated positive urine drug test results mean that the treatment plan is not working and that another approach should be considered. Efforts to reduce the patient's substance use by monitoring drug test results work best in conjunction with open communication between the practitioner and the patient.

Monitoring treatment compliance is a trust issue, and trust is important for the development of the therapeutic alliance. The practitioner needs to create an environment in which the patient feels safe to report honestly how he or she is progressing in recovery. Relapses are a normal part of the natural history of recovery, and how the practitioner responds to them is essential to building a therapeutic alliance and trust. Getting honest with oneself and others about one's substance use and its impact on one's life is essential to lasting recovery, so honesty is an important ground rule for establishing the patient–practitioner relationship. That said, the practitioner should be clear early on that addiction leads some patients to be dishonest about their drug use, so a policy of "trust yet verify" is used—drug testing and corroboration from family can help verify the patient's reports. The practitioner should express trust in the patient; then, if the patient is not honest about reporting substance use, the practitioner must address the lack of honesty as a therapeutic issue that impedes recovery. If a patient tries to deceive the practitioner, the practitioner should be direct yet empathic: "I know it is hard to stop using. What do you think might help?"

The response to a positive drug screen in patients being treated for an SUD depends on more than one factor, including the types of drugs found in the test. If positive results

continue and the patient is not progressing, the patient may need referral to more intensive treatment. However, if the patient readily admits to a relapse and seems fully committed to continuing treatment, the practitioner should support the patient's recommitment to recovery. Each patient needs to be assessed as an individual. If the patient is receiving medication-assisted treatment, the dosage may need to be increased.

An important concept of substance abuse treatment is that one failure (e.g., relapse, leaving treatment), or even multiple treatment failures, is not a reason to deny further treatment to a patient. The practitioner should expect relapses and be prepared to respond in a therapeutically appropriate manner. The patient may not be able to achieve recovery after one, or even several, treatment periods. SUDs are chronic, relapsing conditions that often need repeated interventions or treatments before a patient is stabilized. The practitioner should not expect that patients with problems related to alcohol and drug use will have any less difficulty than other patients in making significant lifestyle changes.

Unless a practitioner is testing for all substances (which is virtually impossible), heavy reliance on drug tests can be misleading in monitoring abstinence. Patients can abstain from their substance of choice while using other substances that may not be part of a particular drug test panel. Practitioners should test not only for the patient's substance of choice, but also other commonly abused drugs. In general, the practitioner should avoid using drug testing as a punitive measure. A cooperative practitioner–patient relationship includes trusting the patient's self-report of substance use, with drug testing used to verify reports.

If a patient is currently in treatment for substance abuse at a treatment center, he or she is likely being tested for drug use. In this case, it is cost effective—and in the patient's best interest—for the practitioner to ask the treatment program (with permission from the patient) for drug test results rather than to repeat a drug test.

Monitoring Patients Receiving Opioids for Chronic Noncancer Pain

Urine drug tests are becoming more common to monitor patients receiving chronic opioid analgesics. In pain management, drug tests can be useful, but they need to be used thoughtfully. The plan and reasoning for drug testing for these patients needs to be discussed thoroughly with the patient. Some patients may find drug tests intrusive; others accept the practice. Drug tests tend to be associated with drug abuse treatment and some patients may be offended when asked to participate in drug testing as part of pain treatment.

Drug tests do not monitor therapeutic drug levels; they provide information regarding medication adherence to the prescribed medication and/or the ingestion of illicit drugs. The only exception is the use of serum methadone levels. If the drug test shows the use of illicit drugs in addition to the prescribed medications, the patient needs to be educated regarding the danger of using illicit substances and opioid pain medications and that substance abuse is not helpful to long-term pain management. Some patients may need to be referred to specialists in both addiction and pain management.

To properly interpret urine drug screens, a detailed understanding of the pharmacology of the prescribed opioid and its relationship to the urine-testing technique must be understood by the prescribing provider. A negative test result when a positive one was expected (e.g., pain medication) may also trigger patient resistance or feelings of guilt, shame, or anger. In these cases, it is important that the practitioner avoid arguing with the patient and remain nonjudgmental. For more information, see TIP 54: *Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders* (SAMHSA, 2012).

Ensuring Confidentiality and 42 CFR Part 2

The concern about the adverse effects that negative attitudes about SUDs and discrimination have on patients in recovery—and how those adverse effects might deter people from entering treatment—led the U.S. Congress to pass legislation and the Department of Health and Human Services (HHS) to issue a set of regulations to protect information about patients' substance abuse. The law is codified at 42 United States Code §290dd-2. The implementing Federal regulations, "Confidentiality of Alcohol and Drug Abuse Patient Records," are contained in 42 CFR Part 2 (Vol. 42 of the Code of Federal Regulations, Part 2). The law and regulations severely restrict communications about identifiable patients by "programs" providing substance use diagnosis, treatment, or referral for treatment (42 CFR §2.11). These rules are stricter than the general Health Insurance Portability and Accountability Act of 1996 (HIPAA) rules about disclosure of personal health information. Under HIPAA, information can be disclosed without written consent for the purposes of routine clinical care and most administrative functions. Written permission from the patients for these disclosures is generally required by 42 CFR Part 2.

In most primary care settings, 42 CFR Part 2 does not apply. Confusion persists about whether general medical care settings (e.g., primary care clinics, hospital emergency rooms) are subject to the law and related regulations because they provide substance abuse diagnosis, referral, and treatment as part of their services. In 1995, HHS revised the definition of the kinds of programs subject to the regulations, clarifying that the regulations do not *usually* apply to a general medical care facility unless that facility (or person) "holds itself out as providing, and provides, alcohol or drug abuse diagnosis, treatment or referral for treatment" (42 CFR §2.11).

Practitioners should be aware that if a healthcare practice includes someone whose primary function is to provide substance abuse assessment or treatment, and if the practice benefits from Federal assistance (including Medicare or Medicaid payments), that practice must comply with the 42 CFR Part 2 law and regulations and implement special rules for handling information about patients who may have substance abuse problems (CSAT, 1997). Clinicians who use a controlled substance (e.g., benzodiazepines, methadone, buprenorphine) for detoxification or maintenance treatment of an SUD are also subject to this regulation. However, physicians who do not use a controlled substance for treatment (e.g., naltrexone) are not subject to the regulation (SAMHSA, n.d.).

In practices subject to 42 CFR Part 2, the results of a patient's drug test and substance use history are confidential and may not be revealed to a third party without the patient's consent, except in certain circumstances (e.g., if the patient was mandated to treatment). Patients must be told before being tested whether the test results must be reported. In addition, any releases of information must specify that the information cannot be shared with a third party without specific consent of the patient.

Many States offer additional protection to medical information about patients that is as strict or stricter than 42 CFR Part 2. However, each State has its own set of rules, which means that the scope of protection offered by State law varies. Whether a laboratory test result is privileged or protected information may depend upon several factors:

- The type of professional holding the information and whether he or she is licensed or certified by the State;
- The context in which the information was communicated;
- The context in which the information will be or was disclosed; and
- Exceptions to any general rule protecting information.

Which practitioners are covered depends on the State within which the clinician practices. Practitioners should consult with their State medical or substance abuse treatment authorities to ascertain the requirements and regulations in their State. SAMHSA provides a directory of State agencies for substance abuse services located at http://www.samhsa.gov/Grants/ssadirectory.pdf.

For more information, see Appendix B of TIP 24: *A Guide to Substance Abuse Services for Primary Care Clinicians* (CSAT, 1997), and *Confidentiality of Alcohol and Drug Abuse Patient Records Regulation and the HIPAA Privacy Rule: Implications for Alcohol and Substance Abuse Programs* (CSAT, 2005).

Preparing for Implementing Drug Testing

Before starting a drug testing program, it is recommended that the practitioner discuss the needs of the program with the laboratory toxicologist or other knowledgeable laboratory staff. Some important areas to obtain information about and to understand include:

- The strengths and limitations of the different tests;
- Standard collection procedures;
- Possible cross-reactivities with the targeted drugs that could affect test results;
- Limitations of the tests offered by the laboratory;
- Windows of detection for different specimens;
- Confirmatory testing, which can be done automatically, or only with specific request of the practitioner;
- Cutoff levels and whether they are appropriate for clinical purposes; and
- Cost of clinical drug test panels.

When ordering a laboratory test to detect substances of abuse, practitioners and staff need to order the correct test for the substances of interest and complete the required forms accurately. The practitioner needs to know exactly what a test is—and is not—measuring. For example:

- The specific drugs or metabolites that can be detected by the test
- The cutoff concentration used by the laboratory or the point-of-care test (POCT)
- The specific substance, class of substances, cross-reacting drugs, and/or metabolites that may yield a positive test result
- The drugs, drug classes, and/or their metabolites for which the test is being done
- The drugs/drug classes that will not be detected by the test

Collecting Specimens

No matter what the reason for drug testing, collections of specimens have more similarities than differences. As in workplace drug testing, which has specific requirements for collecting samples, clinical drug testing should have established collection procedures for that facility or office that follow the College of American Pathologists, Clinical Laboratory Improvement Amendments, and local and State regulations. A properly collected specimen is essential to a obtaining an accurate test result, whether for a POCT or for a test performed at a laboratory. The person responsible for specimen collection needs proper training. His or her duties include:

- Establishing the identity of the patient;
- Explaining clearly the collection procedure to the patient;
- Ensuring that the collection container is appropriate for the specimen matrix;
- Labeling the specimen properly;
- Collecting a sufficient amount of the specimen;
- Ensuring that the specimen collection method prevents substitution, dilution, or adulteration;

- Preventing contamination from environmental sources when collecting specimens;
- Storing the specimen according to the manufacturer's or laboratory's recommendations (e.g., proper temperature) to maintain specimen integrity;
- Preventing loss of or tampering with specimen by storing it in a secure area;
- Properly recording information; and
- Following universal precautions (e.g., wearing gloves and a mask, proper disposal of contaminated materials).

Collection procedures for drug testing should be conducted in ways that preserve patients' dignity. The procedures should be written and explained to patients before collection. Product inserts should be the basis for written protocols and not used as directions when actually collecting and testing specimens or reporting results.

The results of a drug test will not provide a diagnosis of an SUD.

Conducting POCTs

Personnel assigned to conduct the POCTs need to:

- Have access to current product inserts for the laboratory collection device and for the POCT device, if it is a combined collection and testing device;
- Pay close attention to the instructions provided with the test, particularly regarding timing and reading the results accurately;
- Understand possible cross-reactivities with other substances, especially if they are interpreting the results;
- Assay appropriate positive and negative quality control samples;
- Decide under what circumstances laboratory confirmatory tests will be ordered; and
- Record test results according to the protocols established by the practice.

If a practitioner is giving immediate feedback to a patient—a major benefit of using POCTs— the practitioner needs to be confident about what the test is measuring, its results, and the limitations of the test. POCT manufacturers generally have a technical assistance telephone line to answer questions. Chapter 5 provides details about using urine drug tests for specific drugs, including windows of detection, cross-reactivities, limitations, and special considerations for interpreting results.

Interpreting Drug Test Results

A drug test indicates whether a substance or a prescribed medication is present at levels below (negative) or above (positive) the test cutoff concentration. A test result can reveal that a specimen is negative, positive, adulterated, substituted, or dilute. Generally, drug testing cannot tell the practitioner the amount of drug ingested by the patient, whether a therapeutic level has been achieved (e.g., opioids for pain relief), or frequency of use, nor can it indicate the patient's level of intoxication, impairment, or severity of abuse, when trying to determine whether a patient may have an SUD. The results of a drug test will not provide a diagnosis of an SUD.

When interpreting drug test results, the practitioner must know exactly what a test is—and is not—measuring. The practitioner must consider:

- The purpose of the drug test;
- The limitations of the test used;
- The drugs or drug metabolites being detected and those not being detected;
- Potential cross-reactivities; and
- The limitations of the selected matrix.

Many other factors need to be considered when interpreting drug test results (e.g., specific substance, class of substances, cross-reacting drugs and/or metabolites that may yield a positive result). Drug test results may raise clinical concerns for practitioners, or provide reassurance about patient adherence to treatment. Testing may provide unexpected information, but should never be the sole basis for diagnosis and treatment decisionmaking. Test results should be used to supplement the information obtained from a comprehensive patient interview, the physical examination, and consideration of the patient's overall health.

To appropriately respond clinically, it is important that there be thoughtful consideration of drug test results, especially those that seem unusual for a particular patient or possibly incorrect. Other clinical findings must also be considered as well as drug test results.

Result: Negative Specimen

A negative test result means that a particular substance was not detected at or above the cutoff concentration in the specimen. A negative screening test result is rarely followed by a confirmatory test, but can be done if requested by the practitioner. Laboratories perform confirmatory tests on positive results, either routinely or only for certain drug/drug class positives (e.g., amphetamines, opiates) (White & Black, 2007), depending on the laboratory. It is imperative that the clinician is familiar with the laboratory's practices and procedures for testing.

The practitioner's response to a negative drug test result is based on the patient's diagnosis and reason for testing:

- If the patient is being treated for an SUD, consistently negative results—along with improvement in other areas of the person's life—may warrant a change in level of treatment (e.g., decreased frequency of visits, decreased testing frequency, changing from observed to nonobserved urine collection).
- If the patient is being prescribed medications with addictive potential (e.g., opioids, sedatives), a negative drug test warrants a reassessment that may lead to more frequent drug testing and office visits.

A negative drug test does not necessarily mean the patient has not used a particular substance or taken the prescribed medication. Negative test results can occur if:

- Errors were made in interpretation of the test.
- The patient has induced enzyme levels from smoking or liver disease and eliminates the medication more rapidly than usual (e.g., methadone).
- The patient has a shortened gastrointestinal tract from surgery and does not absorb the drug sufficiently for detection.
- The patient ran out of medication.
- The patient took the medication but not when expected or during the window of detection for the ordered test.
- The patient was thirsty and drank sufficient water to dilute the specimen.
- The patient may have consumed an excessive amount of fluids to deliberately dilute a urine specimen.
- The appropriate test for a particular medication or substance was not performed.
- The cutoff concentration used in the test was set too high, so small amounts of the drug/drug metabolites were missed.
- The parent drug and/or its metabolites were excreted before specimen collection (e.g., outside the detection window).
- The specimen may have been adulterated or substituted.

If a negative confirmatory test result is a surprise based on the patient's self-report, collateral report (e.g., from a spouse or partner, from a parent stating that he or she has found drugs or drug paraphernalia in a child's room), or other evidence, the practitioner should reconsider the testing procedures and assessing the patient's behavior. The practitioner could contact the laboratory and discuss the results with laboratory personnel, especially to see whether the negative report came from values that were just below the laboratory's cutoff concentration. Repeated urine testing could be done, or oral fluid could be tested.

The practitioner could also consider:

- Changing or including additional drugs for which testing is performed based on the information received.
- Adding specimen validity testing or testing the original negative specimen for validity.
- Changing the matrix tested (e.g., test urine instead of oral fluid for a longer detection window), if possible (e.g., based on drug detection period, sensitivity, ease of adulteration/substitution of the specimen).
- Testing repeated serial urines.
- Changing the drug-testing methods (i.e., change from POCT to laboratory test).
- Determining whether the testing occurred outside of the detectable window for the substance.

A confirmed negative test result for a patient receiving a prescribed medication, such as in pain treatment, is of concern. Again, the practitioner should first check with the laboratory about the validity of the test: Was the cutoff concentration low enough to measure therapeutic levels of the medication? In this case, retesting may be appropriate. Was the correct test performed to detect the prescribed substance (e.g., oxycodone is not detected in a standard 5-drug panel)?

If the negative test result is valid for prescribed scheduled medications, the practitioner must decide how to proceed with the patient who is, at best, not adhering to his or her prescribed medication regimen or, at worst, diverting the medication. For many reasons, a negative test should not be used to blame the patient for "diversion" unless there is other credible, incriminating information (e.g., witnessed attempts to sell the medication, drug-seeking documentation from prescription monitoring programs).

Result: Positive Specimen

A positive screening test result means that a particular substance was detected at or above the administrative cutoff concentration in the specimen. Confirmatory tests are frequently performed for specimens with positive screening results. If the patient admits drug use when informed of positive results from a POCT, a confirmatory test is not needed.

False-positive results are possible with screening (initial) tests. If a presumptive positive is confirmed by a second methodology, such as gas chromatography/mass spectrometry (GC/MS) or liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS), a false positive is highly unlikely if the test is performed correctly. If a positive result is surprising and the patient vehemently denies recent or current use, the practitioner should order a laboratory confirmatory test if such a test is not already part of the laboratory's testing agreement.

Interpretation of positive tests can sometimes be complex, especially if a patient is being monitored for abstinence following heavy drug use. With frequent use, significant bodily accumulation of drugs can occur with the consequence that drug metabolite(s) may be excreted for extended periods. This is especially true for highly lipid soluble drugs, such as marijuana (tetrahydrocannabinol) and phencyclidine, but it also applies to other drugs, such as cocaine and heroin. A patient who is recently abstinent may continue to test positive for days to weeks depending upon the drug and pattern of use. Distinguishing this normal pattern of body elimination of

drugs from new drug use can be difficult. Huestis and Cone (1998) have published methods for evaluating creatinine-normalized cannabinoid urine results between two specimens collected at least 24 hours apart to predict new marijuana use. These models were more recently updated and improved to take into account the specific times between two urine collections (Smith, Barnes, & Huestis, 2009). In a similar vein, Preston, Silverman, Schuster, and Cone (1997) developed a model for differentiating new cocaine use from residual cocaine metabolite excretion during abstinence. These criteria are based on established pharmacokinetics of benzoylecgonine and include urine creatinine normalization for control of variations in water intake and excretion.

If the confirmatory test result is positive for nonprescribed substances, the practitioner should review the patient's use of prescribed medications, OTC products, and herbal products to determine whether any of these may be the source of the positive result (e.g., poppy seeds causing a positive for codeine or morphine; high doses of morphine causing a positive for hydromorphone). The practitioner may also retest using a different matrix. However, it is worth noting that changing matrices makes interpretation difficult. Hair provides a longer detection window than do other matrices. If a hair specimen was used for testing, a patient could test positive for drug use, even if he or she has not used the substance for weeks. Segmenting a hair specimen is useful to narrow the window in which a positive is observed. However, hair testing is expensive. A urine or oral fluid drug test could provide a more accurate picture of very recent use. However, if the second specimen using the same or a different matrix is negative, it does not refute the scientific validity of the first test.

Clearly, drug test results should never be the sole criteria used for diagnosis of an SUD or making treatment decisions. The practitioner should not take action based solely on drug test results, but should consider them along with behavioral and physical assessments and any collateral information obtained (with permission of the patient) from a spouse, partner, or family member.

Other possible changes in drug-testing procedures include:

- Increasing the testing frequency to discourage illicit drug use by the patient, or possible diversion of prescribed medications;
- Changing the drugs tested for (e.g., test for another class of drugs) to detect the full scope of the patient's drug use; and
- Changing the drug-testing methods (e.g., use a laboratory test instead of a POCT or request a confirmatory test for all initial tests) to rule out false-positive results.

Other changes to treatment are discussed in the section on monitoring patients in Chapter 4.

Result: Adulterated or Substituted Specimen

Urine is the easiest specimen to adulterate, and commercial formulas of synthetic urine are available for substitution. Other fluids, including water, also have been used for substitution. If the test result indicates that the specimen has been adulterated or substituted, the practitioner collects another specimen and reviews procedures to determine whether the temperature and pH of specimens are being checked immediately after collection. For patients who seem to have several test results of adulterated or substituted urine, stricter collection procedures could be instituted for that patient. These could include:

- Ensuring that adulterants, such as soap, ammonia, or bleach are not readily available in the collection area when that patient provides specimens;
- Prohibiting personal belongings in the bathroom;

- Turning off the source of running water during collection and putting blue dye in the toilet; and
- Observing specimen collection.

The practitioner should review the patient's history, interview the patient, and observe the patient's behavior during the interview. The patient may need to be referred to a more intensive level of care. The drug-testing program can also be modified by adding a specimen validity test to the POCT or laboratory test, and changing the specimen matrix (e.g., oral fluid is least likely to be adulterated).

Dilute Specimen

A dilute urine specimen can be negative or positive, depending upon the degree of dilution and amount of drug excreted. If the test result shows that the specimen has been diluted, the practitioner should discuss both the dilution and the negative or positive test result with the patient. In addition, the practitioner could:

- Test a different matrix, if possible;
- Collect and test a new specimen;
- Review the specimen collection site and ensure that bluing has been added to the toilet, that the water is turned off to the taps, and that patients are not allowed to take personal effects into the bathroom; or
- Consider medical reasons for diluted urine (e.g., conditions, such as routinely receiving diuretics, resulting in polyuria).

Result: Invalid Urine Specimen

An invalid result is one in which scientifically supportable analytical test results cannot be established for a specimen. An invalid laboratory test result for urine can be caused by many factors, such as:

- A physiological inconsistency between the patient's urine creatinine and specific gravity;
- An interference in the screening or initial test analysis;
- An interference in the confirmatory assay;
- The presence of oxidizing compounds at or above a cutoff set by the laboratory;
- A urine pH greater than or equal to 3.0 but less than 4.5 or outside other range set by the laboratory or POCT manufacturer;
- A urine pH greater than or equal to 9.0, but less than 11.0 or outside other range set by the laboratory or POCT manufacturer;
- The presence of nitrites in urine at or greater than 200 µg/mL but less than 500 µg/mL, or above a level set by the laboratory or POCT manufacturer;
- The possible presence of chromium (VI);
- The possible presence of a halogen (e.g., bleach, iodine, fluoride);
- The possible presence of surfactant (e.g., soap);
- The physical appearance of a specimen is such that the laboratory feels analysis of the specimen might damage its instruments; and
- Other factors determined by the laboratory for an invalid specimen.

An invalid test result is not definitive proof of specimen tampering. The practitioner should consider other possible causes before assuming that the patient has attempted to subvert the test. The practitioner could try to determine the reason for the report or discuss

possible causes with the laboratory (e.g., Was an unidentified adulterant suspected? Were the specimen's physical characteristics inconsistent with human urine?). A review of the patient's history may reveal a medical explanation (e.g., a medication that could have interfered with the test).

The practitioner could also have another specimen collected and tested and ensure that the collector follows proper procedures, including restricting patient access to materials that could be used to adulterate or substitute the specimen.

Results are also reported as indeterminate or inconclusive. The practitioner should consider the possible causes, including storage and transport irregularities, and potential medical explanations (e.g., a medication that could have interfered with the test). If this happens often, the practitioner may want to ask the patient to return for further discussion and repeat the test.

Frequency of Testing

Drug testing can be done when conducting an assessment when an SUD is suspected, or as a baseline when prescribing medications with addictive potential. The subsequent frequency of drug testing depends on the practitioner, the individual patient, the diagnosis, and the reason for drug testing.

In opioid pain management, testing can be done both to ensure compliance with prescribed medications and to identify abuse of illicit substances. Drugs of interest in this instance include benzodiazepines and opioids (e.g., oxycodone, methadone, fentanyl, hydrocodone, hydromorphone, morphine). Drug tests can be done before providing initial prescriptions or refills (White & Black, 2007) or for other medications with addictive potential. Testing can also be done if the patient exhibits aberrant behavior, if diversion of prescribed medications is suspected, or randomly to monitor treatment.

For the patient being treated for an SUD, drug tests can be done:

- With changing frequency as the patient progresses (less often as the patient progresses, or more often with lack of progress);
- If relapse is suspected;
- If the patient exhibits aberrant behavior; or
- Randomly to monitor treatment.

For the patients receiving medications, particularly opioids, with abuse potential, drug tests can be done during every visit, randomly, before providing prescription refills, or if the patient exhibits aberrant behavior. The frequency can also change with several drug tests that show that the patient is taking the medication as prescribed and is not positive for illicit drugs.

A drug test may not be needed if the patient admits illicit drug use or treatment noncompliance for prescribed medications when coming to his or her appointment.

Documentation and Reimbursement

Proper documentation is needed for both patient record keeping and to obtain reimbursement.

Documentation

In addition to keeping accurate patient medical records, practitioners must ensure proper documentation of the use of POCTs. This includes (Howerton et al., 2005):

- Written procedures for performing POCTs;
- Inventory control—lot numbers and expiration dates for POCTs;
- Documentation of staff training and reassessment;
- Quality assurance test results;

- Documentation of problems and problem resolution; and
- Copies of laboratory test orders and results.

Patient medical records should document:

- The medical necessity for drug testing;
- Tests performed and test results;
- Changes made to the treatment plan based on test results; and
- Referrals made.

Reimbursement

Testing for alcohol or drugs is billed by the specific biological tests conducted according to the Current Procedural Terminology (CPT) codebook (American Medical Association, 2006). Insurance coverage for alcohol or drug testing varies by carrier. Careful documentation of the need for testing assists with obtaining reimbursement. The current issue of the CPT codebook should be consulted to obtain proper reimbursement.

Some CPT codes that are used for testing include:

- 80100: For qualitative screening tests used to detect the presence of *multiple* drug classes.
- 80101: For qualitative screening tests used to detect the presence of *one* drug class.
- 80102: For each *confirmatory* test.
- 82055: Alcohol testing (any method other than breath).
- 82075: Alcohol testing (breath).

Centers for Medicare & Medicaid Services uses different codes:

- G0430-QW: When multiple drug classes are tested and the testing methodology does not use the chromatographic method
- 80100-QW: When testing for multiple drug classes that do use the chromatographic method
- G0431: Used, per drug class, when performing a test for a single drug class

The medical necessity for testing can be documented by using International Classification of Diseases codes (i.e., harmful use or dependence syndrome) from the *International Statistical Classification of Diseases and Related Health Problems, Volume 1: 10th Revision* (World Health Organization, 1992). However, the patient may want to pay for a drug test and not submit the cost to the health insurance company. This should be discussed with the patient.

Chapter 5—Urine Drug Testing for Specific Substances

In This Chapter

- Window of Detection
- Specimen Collection
- Adulteration, Substitution, and Dilution
- Cross-Reactivity
- Alcohol
- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine
- Marijuana/Cannabis
- Opioids
- Other Substances of Abuse

Urine is the most rigorously evaluated and most commonly used matrix for drug testing (Watson et al., 2006). All results are affected by laboratory test or point-of-care test (POCT) cutoff concentrations. Therefore, practitioners should always consult with laboratory staff when ordering laboratory tests or carefully read POCT package inserts before using the test. Numerous POCTs are available for urine drug testing.

Window of Detection

The window of detection for urine falls in the intermediate range, compared with the detection period or window for other matrices. Many factors influence the window of detection for a substance. Factors include, but are not limited to, the frequency of use (chronic or acute), amount taken, rate at which the substance is metabolized, cutoff concentration of the test, patient's physical condition and, in many cases, body fat. Some hepatic, renal, endocrine, and other pathologies may extend the detection window.

Drugs are present in urine from within minutes of use to several days after, depending on the substance; quantity ingested; the degree to which the bladder was filled with drug-free urine at the start of drug use; the patient's hepatic, cardiac, and renal function; the patient's state of hydration; and drug type. Drugs that are smoked or injected are detectable in urine samples almost immediately. Detection rates for drugs taken orally are slower, taking up to several hours and peaking at about 6 hours (Dolan et al., 2004).

The window-of-detection estimates used in this chapter are from several sources: Cone (1997), Dasgupta (2008), Verstraete (2004), Warner (2003), White and Black (2007), Wolff et al. (1999), and Wong and Tse (2005).

Many urine drug tests detect the drug metabolite, rather than the drug itself. As a general rule, drug metabolites remain in the body for a longer period than does the parent drug, allowing for a longer detection period. For example, when the test is for cocaine using urine, the target compound is usually the metabolite, benzoylecgonine, rather than the parent cocaine molecule.

It may be difficult to detect illegal substances in urine specimens of patients who stop use for several days before providing a specimen. Most substances of abuse are detectable in urine for approximately 2–4 days (Center for Substance Abuse Treatment [CSAT], 2006b; Cone, 1997). However, the detection time may be prolonged when large, frequent doses are taken over a long period (CSAT, 2006b). For example, one dose of intranasal cocaine may be detectable in urine for 3–5 days using a cutoff of 300 ng/mL after ingestion, but daily, heavy cocaine use may be detected for additional days following discontinuation of use (Verstraete, 2004). Chronic use of marijuana may be detectable for up to 30 days after use is stopped.

Specimen Collection

Urine collection usually is easier than collecting blood, and samples are available in sufficient quantities (Warner, 2003). Urine sample collection is not usually observed in primary care settings. Clinical drug testing usually does not warrant direct observation that may be necessary in forensic or substance abuse treatment program testing. However, if it is suspected that a patient is tampering, diluting, or adulterating urine specimens, some measures used in forensic or workplace testing can be used to prevent this, including:

- Directly observing specimen provision;
- Turning the water off to the taps and adding a bluing agent to the toilet tank to avoid sample dilution;
- Not providing hand soap in the restroom where the sample is being done;
- Not storing cleaning agents in the restroom (e.g., ammonia-containing products, bleach, toilet cleaning products); and
- Not allowing coats, purses, or bags into the restroom with the patient.

Patients who exhibit "shy bladder syndrome" (inability to void) may need to consume liquids to provide a specimen (e.g., 8 oz. of water every 30 minutes, but not to exceed a maximum of 40 oz. over a period of 3 hours, or until the patient has provided a sufficient urine specimen).

Once the specimen is collected and labeled:

- The appearance and color of the urine sample should be documented.
- The use of primary collection containers with a temperature-sensitive strip on the outside is recommended, rather than placing a thermometer or temperature strip into the urine.
- The urine specimen temperature should be recorded within 4 minutes of collection; the temperature should be between 90°F and 100°F.

Additional clinical testing, such as a routine urinalysis (e.g., pH and tests to detect the presence of oxidizing components and adulterants) can be conducted on an aliquot separate from that used for urine drug testing to avoid any argument that a positive was the result of a foreign object being placed in the patient's urine specimen.

Adulteration, Substitution, and Dilution

Urine tests can be reported as adulterated, substituted, or dilute.

Adulteration

An adulterated urine specimen is one containing a substance that is not normally found in urine or that is normally found, but is in abnormal concentrations. In vitro adulterants are foreign substances added to the urine specimen after voiding. Adulterants work by interfering with immunoassay and/or confirmatory assay function, or they convert the target drug to compounds not

detected by the test (Jaffee, Trucco, Levy, & Weiss, 2007). Ordinary household products (e.g., laundry bleach, toilet bowl cleaner, hand soap, vinegar, ammonia, eye drops) have been used for many years to adulterate urine specimens to obtain a negative drug test result (Dasgupta, 2007). Household products that alter the pH of urine to a value outside the physiologic range can be easily detected by determining the pH of the sample (Dasgupta, 2007). Products such as bleach and other oxidizing agents can be detected with a general oxidants assay.

Numerous types of commercial adulterants are available via the Internet. The following list is a summary of such products by active ingredient (Jaffee et al., 2007):

- Glutaraldehyde (e.g., "Clean X") can interfere with absorbance rates on immunoassay tests, masking the presence of substances such as the marijuana metabolite, 11-nor-9-carboxy-THC (THCCOOH), opioids, cocaine metabolites, morphine, amphetamine, phencyclidine (PCP), and most other immunoassay tests. The presence of glutaraldehyde usually is detected by observing abnormal immunoassay results; however, other substances can also cause an abnormal immunoassay result.
- Sodium or potassium nitrite (e.g., "Klear," "Whizzies") can mask the presence of marijuana metabolite in immunoassay tests and the presence of THCCOOH in confirmatory tests. Abnormal nitrites in urine can be detected by a specific nitrites assay or in a general oxidants assay.
- Pyridinium chlorochromate (PCC, commercially known as "Urine Luck") is an oxidizing agent that masks the presence of THCCOOH and, depending on the pH of the urine, can affect test results for morphine. Cocaine metabolites, amphetamine, and PCP are not affected by PCC (Dasgupta, 2007). Chlorochromate and other oxidizers, such as dichromate, can be detected in urine using a general oxidants assay.
- Peroxide/peroxidase (e.g., "Stealth") can oxidize drugs and their metabolites, making THCCOOH and lysergic acid diethylamide (LSD) undetectable by immunoassay tests. The peroxide/peroxidase combination may be difficult to detect in urine that is not fresh because both hydrogen peroxide and peroxidase tend to degrade with time.

The effectiveness of an adulterant depends on the amount of the adulterant added and, in some instances, the concentration of the drug in the sample. Specimen validity tests can detect many adulterants in addition to those described above.

Substitution

Synthetic urine products can be submitted when collection of a urine specimen is not observed. These products are premixed liquids with the characteristics of natural urine (i.e., correct pH, specific gravity, and creatinine levels). To achieve the temperature of recently voided urine, synthetic urine products can be heated in a microwave or taped next to a heating pad in a pocket. Sometimes, another person's urine is submitted.

More commonly, water or a saline solution is substituted for urine. Thus, a urine specimen is considered substituted when the creatinine concentration on both the initial and the confirmatory tests is less than 2.0 mg/dL and the specific gravity is less than or equal to 1.0010 or greater than or equal to 1.0200 (Substance Abuse and Mental Health Service Administration [SAMHSA], 2010b).

Dilute Specimens

Diluting the urine sample to the point where the targeted drug is below the cutoff concentration is another way to obtain a negative test result. For instance, consuming water in more-than-normal quantity and taking diuretics can dilute the urine sample. Individuals may also add water from the tap or toilet bowl to dilute specimens if tap

water is available in the restroom and/or bluing has not been added to the commode water. Commercial products are available that promise to "cleanse the urine." These products advocate consuming large amounts of tea or other fluids, increasing urine volume, thereby diluting drugs in the urine. Reducing the amount of time between notice that a specimen will be collected and the time of collection reduces the potential for the patient to consume enough fluids to dilute the urine.

A laboratory will report a urine specimen as dilute in conjunction with a positive or negative drug test when the creatinine concentration is greater than or equal to 2 mg/dL and less than 20 mg/dL, and the specific gravity is greater than 1.0010 and less than 1.0030 (SAMHSA, 2010b). Dilution may raise suspicion of tampering, but does not necessarily confirm tampering. Other factors need to be considered, such as whether the patient is taking a diuretic, eating a strict vegetarian diet, or maintaining a high state of hydration. Other factors include whether the patient was working in hot weather conditions and drank large amounts of fluid or drank fluids immediately before providing the specimen.

Cross-Reactivity

The cross-reactivity of urine immunoassay tests varies by drug class. For example, tests for cocaine measuring its principal metabolite, benzoylecgonine, have low cross-reactivity with other substances. However, tests for amphetamine/methamphetamine usually are extremely cross-reactive, and further laboratory testing using a method different in principle from immunoassay (i.e., not a second immunoassay) is required to confirm amphetamine use (Gourlay et al., 2010). As stated above, cross-reactivity is many times viewed as a negative aspect of immunoassay. However, cross-reactivity does have a positive side. An immunoassay that is specific for morphine will detect only morphine and will miss other opiates (e.g., hydrocodone) that a patient might be using without the treating physician's knowledge. Thus, a general opiates screen is preferred over a specific test when looking for opiate-type drugs. Lack of cross-reactivity also may affect testing, such as that performed for oxycodone, as discussed under "opioids."

Alcohol

The window of detection for alcohol is 7–12 hours. The frequency of alcohol use minimally affects the window of detection; however, ingestion of large amounts results in a longer detection time in body fluids than ingestion of a small amount of alcohol. The metabolism of ethanol may be accelerated in people who use chronically or binge. Approximately 90–95 percent of alcohol is oxidized in the liver before elimination in the urine, and only 1–2 percent of ingested alcohol is excreted unchanged in the urine (Moeller, Lee, & Kissack, 2008). Because of this rapid metabolization, blood tests or the standard hand-held breath devices (breathalyzers) are often used, and in clinical settings, urine alcohol tests are used far less frequently than are blood tests.

Urine can be analyzed for alcohol through chemical assays, enzyme immunoassays, or gas-liquid chromatography (GLC), with the most accurate reading produced by GLC. Urine drug tests for alcohol indicate only recent ingestion; they cannot identify long-term abuse. Furthermore, a urine ethanol can show use prior to the collection of the urine specimen only within a reasonable timeframe. Alcohol in blood or a blood product (e.g., serum, plasma) or a breath alcohol is required to show impairment and the degree of impairment.

Biomarkers, such as the gamma-glutamyl-peptidase, carbohydrate-deficient transferrin, aspartate amino transferase (measured in serum), and erythrocyte mean cell volume tests may confirm a suspicion of long-term alcohol abuse or dependence. Ethyl glucuronide EtG) and ethyl sulfate are direct metabolites

of ethanol that can be measured in urine. Testing for EtG is becoming more common to monitor alcohol consumption for people who have been ordered to abstain. However, more research is needed to establish standards to rule out possible exposure to alcohol in commercial products, such as mouthwash and hand sanitizers, versus drinking of alcoholic beverages (CSAT, 2006a). More information about biomarkers for alcohol use disorders is in *The Role of Biomarkers in the Treatment of Alcohol Use Disorders* (CSAT, under revision).

Amphetamines

The SAMHSA workplace cutoff concentration for amphetamines is 500 ng/mL for initial testing, and 250 ng/mL for confirmatory testing. To be reported positive for methamphetamine, a specimen must also contain amphetamine at a concentration equal to or greater than 100 ng/mL (SAMHSA, 2008).

The window of detection varies. A single dose of amphetamine or methamphetamine can be detected in the urine for approximately 24 hours, depending upon urine pH and individual metabolic differences. People who use chronically and at high doses may continue to have positive urine specimens for 2–4 days after last use (SAMHSA, 2010b). Methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), and methylenedioxyethylamphetamine (MDEA) can be detected for 1–2 days (Moeller et al., 2008; SAMHSA, 2010b).

Drug tests for the presence of amphetamine are among the hardest to interpret. Methamphetamine is the target analyte for amphetamine/methamphetamine testing. Immunoassay tests are highly cross-reactive and may detect other sympathomimetic amines, such as pseudoephedrine, readily available as over-the-counter (OTC) products. Structural similarities of many OTC products—including diet agents; decongestants; and several prescription medications, such as those to treat attention deficit/hyperactivity disorder, narcolepsy, and Parkinson's disease, or to suppress appetite—can cause initial positive test results. Adderall is an amphetamine and will result in a positive test for amphetamine.

Methamphetamine exists as two optical isomers (stereoisomers) that are designated *d*- and *l*-. The *d*-form has high abuse potential. The *l*-form in therapeutic doses has a primarily peripheral action and is found in some OTC products (Kwong, 2008a, 2008b). Immunoassay tests for amphetamine and methamphetamine can be divided into two types: (1) those designed to detect amphetamine and methamphetamine, only; and (2) those that also have variable cross-reactivities with "designer amphetamines," such as MDA, MDMA, and MDEA, as well as with sympathomimetic amines (e.g., ephedrine, phentermine, pseudoephedrine, phenylpropanolamine) (Kwong, 2008a, 2008b).

Typical immunoassay tests do not distinguish methamphetamine and/or amphetamine use from use of OTC products containing sympathomimetic amines. All presumptively positive urine "amphetamines" results should be confirmed by an alternate methodology different in principle from the immunoassay used to produce the screening result (White & Black, 2007). A confirmed test by gas chromatography/mass spectrometry (GC/MS) for methamphetamine can either be *d*-methamphetamine (licit or illicit) or OTC nasal spray. A confirmed test for methamphetamine is insufficient to distinguish illicit drug use from use of an OTC product. A separate test is available that is offered by most laboratories that distinguishes illicit methamphetamine (*d*-methamphetamine) from OTC nasal inhaler (*l*-methamphetamine). This specialized confirmatory test, stereospecific chromatography, is necessary to distinguish methamphetamine, amphetamine, and their isomers from legitimate sympathomimetic agents (Gourlay et al., 2010). However, a result confirmed by a second methodology,

such as GC/MS, is definitively amphetamine and/or methamphetamine. Cross-reactivity with MDMA, MDA, and/or MDEA is beneficial in that, once confirmed by an alternate methodology, it may uncover a previously unsuspected substance abuse problem.

Patients should be advised to avoid the use of this type of OTC nasal spray when being tested. A confirmed test for amphetamines or methamphetamines can occur because a number of other prescription medications metabolize to these isomers. The patient needs to be questioned regarding the reasons for taking the medication to determine whether it is by prescription or is being misused.

Tests for amphetamine cross-react with several other substances and are too numerous to present a comprehensive list. A confirmed test for amphetamine or methamphetamine can occur because a number of other medications metabolize to these. The product inserts should be consulted for the current list of cross-reacting drugs. Substances known to metabolize to methamphetamine and amphetamine include benzphetamine, dimethylamphetamine, famprofazone, fencamine, furfenorex, and selegiline (SAMHSA, 2010b). Substances known to metabolize to amphetamine include amphetaminil, clobenzorex, ethylamphetamine, fenethylline, fenproporex, mefenorex, mesocarb, and prenylamine (SAMHSA, 2010b).

Barbiturates

The incidence of barbiturate abuse is low compared with abuse of other drugs or alcohol (SAMHSA, 2009). Barbiturates (sans phenobarbital) are detected easily using a variety of immunoassays, even though only a small amount of the parent drug is found in the urine. The use of barbiturates may be confirmed readily using several different methods including, but is not limited to, GC/MS and liquid chromatography/tandem mass spectrometry (LC/MS/MS) due primarily to the high doses commonly administered or taken (Levine, 2010). Most urine immunoassay tests use secobarbital as the calibrator, at a cutoff concentration of 200 ng/mL or 300 ng/mL. Cross-reactivity with other barbiturates varies with this assay, and the detection window is dose dependent. Several commonly used assays generally cross-react with and detect butabarbital and amobarbital (Kwong, 2008b). The window of detection depends on the type of barbiturate (see Exhibit 5-1).

Benzodiazepines

The results of urine drug tests for benzodiazepines may be challenging to interpret without a basic knowledge of the pharmacokinetics of the different benzodiazepines. Like barbiturates, benzodiazepines are classified by their elimination half-lives. It is important to know a test's sensitivity and specificity for the benzodiazepine in question. False-negative results can occur if a test is set to detect only one benzodiazepine or its primary metabolite(s), and the clinician is trying to monitor a non-cross-reacting benzodiazepine. Because the parent drug in the benzodiazepine class is usually undetectable in urine drug tests, drug-screening immunoassay tests are

Exhibit 5-1. Barbiturates—Window of Detection

Selected Barbiturates	Window of Detection
Short acting (e.g., pentobarbital, secobarbital)	4–6 days after the last use (cutoff of 300 ng/ml)
Intermediate acting (e.g., amobarbital, butabarbital)	3–8 days (cutoff of 300 ng/mL)
Long acting (e.g., phenobarbital)	10–30 days at a cutoff of 300 ng/mL

Sources: Baselt (2008); White & Black (2007).

usually designed to detect a specific metabolite, either unconjugated oxazepam or its glucuronide conjugates. Immunoassay tests are more likely to detect benzodiazepines that are metabolized to the targeted compound and may miss the other non-cross-reacting compounds.

Benzodiazepines can be divided into several groups, based on their metabolites:

- Some benzodiazepines (e.g., chlordiazepoxide, diazepam, temazepam) are metabolized to oxazepam. Oxazepam is conjugated into an inactive glucuronide metabolite.
- Nitrobenzodiazepines (e.g., clonazepam which is primarily reduced to 7-aminoclonazepam, which is further metabolized) are usually reduced to the corresponding amino compound, but are not converted into oxazepam or its conjugate.
- The triazolobenzodiazepines such alorazepam, estazolam, and triazolam tend to form hydroxyl derivatives that are separate and distinct from oxazepam.
- Other benzodiazepines (e.g., lorazepam, flurazepam) have a unique metabolism that does not result in the formation of oxazepam.

Clinical laboratories usually use cutoff concentrations of 200 ng/mL or 300 ng/mL, which can detect use of a benzodiazepine, but may not necessarily detect a low therapeutic dose (e.g., triazolam) (Warner, 2003).

Flunitrazepam (Rohypnol), commonly known as "Roofies," is a Schedule I substance. Flunitrazepam is one of the so-called "date-rape" drugs and shows good to excellent cross-reactivity in most commercial urine benzodiazepine assays except the Neogen, Immunalysis, and Randox assays. If ingested, flunitrazepam and/or its metabolites may be detected for approximately 4–12.5 days at higher doses (White & Black, 2007). See Exhibit 5-2 for estimated windows of detection of some of the most commonly prescribed benzodiazepines.

Cocaine

The Federal workplace cutoff concentration for initial testing for cocaine is 150 ng/mL, and confirmatory testing for cocaine metabolite (benzoylecgonine) is 100 ng/mL (SAMHSA, 2008).

Urine drug tests for cocaine detect cocaine's major metabolite, benzoylecgonine. The body quickly metabolizes cocaine to its major metabolite, benzoylecgonine, and neither is stored in the body. Therefore, even with chronic use, the window of detection is 1–3 days (Jufer, Walsh, Cone, & Sampson-Cone, 2006), with the clinical test cutoff of 300 ng/mL. The detection window may be longer using the federally mandated cutoffs.

Urine immunoassay tests for cocaine are highly specific and detect use of powder (snorting or insufflation), parenteral use, oral ingestion, smoked, or use of crack cocaine. Among the possibilities of products they

Exhibit 5-2. Benzodiazepines—Window of Detection*

Benzodiazepines	Estimated Window of Detection
Short acting (e.g., triazolam):	Up to 24 hours
Intermediate acting (e.g., alprazolam, clonazepam, lorazepam, temazepam):	1–12.5 days
Long acting (diazepam):	5–8 days for diazepam 6–24 days for the active metabolite, nordiazepam
Chronic abuse of benzodiazepines	Up to 30 days after the last dose

*Higher doses and some pathologies may extend the window of detection

Source: White & Black (2007).

cannot distinguish is "Inca" tea or "coca" tea—made from coca leaves—because they contain cocaine. Ingestion of tea prepared from coca leaves produces positive urine tests for benzoylecgonine (Jenkins, Llosa, Montoya, & Cone, 1996).

Immunoassay tests are highly specific for the cocaine metabolite (benzoylecgonine) and do not cross-react with other substances.

Marijuana/Cannabis

The SAMHSA workplace cutoff concentration for cannabinoid metabolites is 50 ng/mL for initial testing. The confirmatory testing cutoff for cannabinoid metabolite (delta-9-tetrahydrocannabinol-9-carboxylic acid) is 15 ng/mL.

Marijuana, the most commonly used illicit drug, can be detected for prolonged periods after regular use. The active principle of marijuana, tetrahydrocannabinol (or THC) has high lipid solubility. The THC that is stored in fatty tissue gradually reenters the bloodstream at very low levels, permitting metabolism and eventual excretion. THC is metabolized extensively in the liver.

The window of detection is highly dependent on the quality of the marijuana, the individual's body fat content and metabolism, chronicity of use, the individual's state of hydration when the urine sample is collected, and the cutoff used by the laboratory (White & Black, 2007). Approximate window of detection times are as follows:

- Up to 3 days for single use
- Up to 4 days for moderate use
- Up to 10 days for heavy use
- 30–36 days for chronic, heavy use

Marijuana is easily detected by immunoassay. Generally, laboratory tests for marijuana use are designed to detect THC-COOH (11-nor-Δ9-tetrahydrocannabinol-9-carboxylic acid; commonly referenced as THC acid or THCA), the major inactive metabolite of THC. Laboratory tests are available with cutoff concentrations of 20 ng/mL, 50 ng/mL, or 100 ng/mL, although the majority of laboratories employ 50 ng/mL. The 20 ng/mL cutoff is commonly used clinically (White & Black, 2007). The 100 ng/mL cutoff is rarely used due to its lack of sensitivity.

Confirmation by GC/MS tests should be performed if the positive screening test results have legal or other serious implications for the patient. Some legal food products are made from hemp seeds (e.g., hemp seed oil, flour, liquor, ale). These products do not appear to be psychoactive, but, after a person has ingested these food products, THC metabolites have been detected in urine specimens. However, usually the THC concentrations in the food products are too low to produce a positive urine drug test result (Bosy & Cole, 2000). Some proton-pump inhibitors have caused positive tests on immunoassay (Gourlay et al., 2010).

The literature is mixed on the test results of passive exposure to marijuana. Under extreme conditions (e.g., the person rides in a closed car with people smoking marijuana), passive exposure can lead to positive results with a screening cutoff of 20 ng/mL. However, the levels of marijuana metabolites found in urine under less extreme passive exposure conditions are below the 50 ng/mL (employment-related) cutoff concentrations and would not be detected (Cone et al., 1987; Perez-Reyes, Di Guiseppi, & Davis, 1983). Marinol and Sativex cause positive results because they contain THC.

Opioids

Clinical urine opioid drug testing is done to detect illicit opioid use, monitor adherence to pain treatment with opioids (especially in pain management clinics), and monitor adherence to methadone treatment. Practitioners need to be particularly careful when interpreting urine drug test results

for opioids. It is essential to understand the metabolism of this class of drugs to interpret drug tests.

The term *opioids* includes both opiates and opioids. Opioids are a group of compounds that have pharmacological properties similar to morphine and have affinity toward the opiate receptors in the brain (Dasgupta, 2008). The term *opiates* refers to naturally occurring alkaloids (morphine and codeine) obtained from the opium poppy and semisynthetic alkaloids that are partially derived from the opium poppy (i.e., buprenorphine, dihydrocodeine, heroin, hydrocodone, hydromorphone, levorphanol, oxycodone, and oxymorphone) (Dasgupta, 2008). Opioids include the synthetic compounds that are structurally unrelated to morphine (i.e., fentanyl, meperidine, methadone, pentazocine, propoxyphene, tramadol) (Dasgupta, 2008).

Opiate immunoassay tests were originally designed to detect morphine and codeine as target analytes to identify heroin use (Kwong, 2008a, 2008b). Morphine is a metabolite of heroin (Warner, 2003). Many laboratories use SAMHSA's Federal workplace cutoff concentrations for opiates and test for morphine, codeine, and 6-acetylmorphone (6-AM). However, for opiates, a cutoff of 300 ng/mL is commonly preferred clinically (White & Black, 2007). As heroin is metabolized, 6-AM is produced, which is then hydrolyzed to morphine. Thus, the detection of 6-AM in the urine proves heroin use, but 6-AM is eliminated quickly from the body, making detection in urine possible for only a few hours (Gourlay et al., 2010). A typical opiate screen reports the presence of only codeine and morphine. An expanded opiate panel may also include hydrocodone and hydromorphone and/or oxycodone and oxymorphone (see Exhibit 5-3).

Distinguishing between illicit opioid use and the use of prescribed opioid medications can be difficult. Immunoassay tests have variable cross-reactivity with semisynthetic opioids (i.e., hydrocodone, hydromorphone) and may or may not detect their use. The synthetic opioids (e.g., meperidine, fentanyl, methadone) are structurally dissimilar enough from morphine that they are not detected in standard opioid urine immunoassay tests, although some cross-reactivity—especially with the metabolites—may exist. Separate immunoassay tests specifically designed for their detection must be used. Oxycodone and its active metabolite, oxymorphone, require a drug-specific test. Specific assays for oxycodone are available as both POCTs and laboratory tests. Specialized tests for synthetic opioids must be ordered when

Exhibit 5-3. Opioids—Window of Detection*

Opioid	Window of Detection	Cutoffs
Buprenorphine	Up to 4 days	0.5 ng/mL
Codeine	1–2 days	300 ng/mL
Heroin metabolite (6-acetylmorphine (6-AM)	1–3 days	10 ng/mL
Hydrocodone	1–2 days	100 ng/mL
Hydromorphone	1–2 days	300 ng/mL
Methadone (maintenance dose)	3–11 days	300 ng/mL
Morphine	1–2 days	300 ng/mL
Oxycodone (immediate-release formulation)	1.0–1.5 days	100 ng/mL
Oxycodone (controlled-release formulation)	1.5–3 days	100 ng/mL
Oxymorphone (immediate-release formulation)	1.5–2.5 days	100 ng/mL
Oxymorphone (extended-release formulation)	1.0–4 days	100 ng/mL

*Higher doses and some pathologies may extend the window of detection.

Sources: Kronstrand et al. (2008); White & Black (2007).

concerns exist about abuse or diversion of synthetic opioid pain medications or to monitor patients' use of buprenorphine or methadone. Many laboratories have specific pain medication panels that test for codeine, morphine, hydrocodone, hydromorphone, oxycodone, fentanyl, and buprenorphine (Gourlay et al., 2010). Buprenorphine has potential for abuse, especially in the stand-alone preparation—Subutex (Smith, Bailey, Woody, & Kleber, 2007).

Poppy seeds can contain morphine and codeine. Ingesting large amounts of poppy seed or products containing poppy seeds can cause a positive urine drug test result. The urine drug test result will show that morphine and, possibly, codeine are present, and the practitioner needs to determine whether poppy seeds are the source. The original employment-related and clinical cutoff concentration for morphine and codeine was 300 ng/mL, but was increased to 2,000 ng/mL to avoid positive test from poppy seed consumption (often cited as the "poppy seed defense"). This higher cutoff minimized opioid-positive test results from poppy seeds, but also reduced the likelihood that opioid use would be detected.

Methadone is a synthetic opioid used for treatment of opioid dependence and chronic pain and is not detected in standard opioid drug tests. Specific tests for methadone and its major metabolite EDDP (or 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) exist and are used to monitor adherence to medication-assisted treatment and to check for illicit drug use. These methadone immunoassay tests have little cross-reactivity with other opioids. Therefore, a positive opioid drug test result for a patient on methadone suggests the use of other opioids. The cutoff concentration is generally set at 300 ng/mL and can detect methadone in urine for several days after the last therapeutic dose. To confirm that the patient has taken methadone and is not simply adding it to a urine specimen, the test for the methadone metabolite, EDDP, can be ordered. If a practitioner is caring for a patient on methadone maintenance treatment for opioid dependence, the practitioner can ask the patient to sign a release of information to obtain the patient's urine test results from the opioid treatment program.

Other Substances of Abuse

Testing information for other substances is presented below.

PCP

The SAMHSA revised workplace cutoff concentration for PCP is 25 ng/mL for initial testing. The confirmatory testing cutoff for PCP is 25 ng/mL. This cutoff is often used for clinical purposes, as well. Federally regulated laboratories are required to test for PCP; other laboratories are not. Directors of clinical laboratories may add PCP to their screening drug panel if PCP use is prevalent in the community. The window of detection for PCP from casual use is 1.5–10 days (urine pH-dependent) and for up to several weeks with chronic use. The metabolite of dextromethorphan can cross-react with PCP and could cause a false positive.

When used to adulterate urine specimens, table salt, sodium hypochlorite, sodium hydroxide, detergent, and soap cause false-negative test results (Jaffee et al., 2007). However, these adulterants can be detected if the pH and specific gravity of the urine samples are checked.

Club Drugs

Club drugs generally include gamma-hydroxybutyrate (GHB), ketamine, flunitrazepam (Rohypnol, or "Roofies"), MDMA, MDA, and MDEA. Urine drug screening tests do not generally screen for club drugs. However, please see the section above on amphetamines for information about MDMA, MDA, and MDEA, and the section on benzodiazepines for information on flunitrazepam (Rohypnol, or "Roofies"). New drug tests may screen for some club drugs,

but routine drug tests cannot detect ketamine or GHB. Testing for GHB can be done by using GC or high-performance LC (LeBeau et al., 2006). The window of detection for GHB is generally less than 12 hours. Two commercial enzyme-linked immunosorbent assays (ELISAs) that test for ketamine are available (Huang et al., 2007). For a single dose of ketamine, detection is possible for about 3 days at a cutoff of 50 ng/mL (Baselt, 2004; Cone & Huestis, 2007).

LSD

Very little of the parent drug, LSD, is excreted in urine and it can be detected for only approximately 4 hours. The most abundant metabolite is nor-LSD (N-desmethyl-LSD), which is generally detected at a cutoff level of 0.5 ng/mL. Confirmatory testing is usually done with LC/MS or LC/MS/MS.

Inhalants

No standard drug test can detect inhalant use. Most inhalants contain many compounds, and no single assay can test for all of them. Some laboratories can test for inhalants using specially ordered tests, primarily with GC. Collection of a specimen for inhalants requires that the specimen be appropriately and rapidly sealed to ensure that the volatile inhalants are not lost.

Toluene is the main substance in many inhalants. It is cleared from the body quickly, leaving a short period to detect exposure. Most laboratories are unable to test for this substance. Urinary hippuric acid (UHA) measurements can be adapted to detect toluene inhalation, but they should be used cautiously because a person's metabolism can raise the levels of UHA. Thiesen, Noto and Barros (2007) report that UHA levels higher than 3.0g/g creatinine indicate intentional exposure.

Appendix B—Laboratory Initial Drug-Testing Methods

Testing Method	Description	Advantages	Disadvantages/ Cautions
Cloned Enzyme Donor Immunoassay (CEDIA)	• An immunoassay using enzyme (ß-glucuronidase) fragments engineered by recombinant DNA techniques. • Two fragments, the enzyme donor and enzyme acceptor, are inactive when separated. • Based on competition for antibody binding sites between drug conjugated with enzyme donor (ED) and drug in the specimen. • Enzyme activity decreases when the ED drug fragment is bound, so the drug concentration in the specimen can be measured by an increase of enzyme activity.	• Same reliability as EMIT in screening for barbiturate use.	• May produce false-positive results for amphetamines and lysergic acid diethylamide when bupropion is used.
Enzyme-Multiplied Immunoassay Technique (EMIT)	• An immunoassay based on competition for antibody binding sites between drug in the specimen and drug labeled with an enzyme. • Enzyme activity decreases on binding to the antibody, so the drug when present in the specimen can be measured by an increase in terms of enzyme activity.	• Widely used. • Simple to conduct (same as CEDIA or KIMS).	• Poor performance record (high rate of false-positive results in some studies). Many over-the-counter (OTC) preparations can cause false-positive results for amphetamines and phencyclidine (PCP) assays.
Enzyme-Linked Immunosorbent Assay (ELISA)	• A competitive binding enzyme immunoassay using drug-specific antibodies immobilized on the sides of a microplate well.	• The most versatile and commonly used immunoassay. • Customized tests developed for different settings, substances, purposes, and matrices.	• Labor intensive. • Poorly suited for automation.

Testing Method	Description	Advantages	Disadvantages/ Cautions
Fluorescence Polarization Immunoassay (FPIA)	• An immunoassay based on competition between the drug in the specimen and drug labeled with a fluorophore. • Light emitted by the fluorescently labeled drug/antibody complex is more polarized. • The specimen's fluorescence polarization value is inversely related to the drug concentration.	• Sensitive. • Specific.	• Cannot be automated conveniently.
Kinetic Interaction of Micro-particulates in Solution (KIMS)	• An immunoassay based on the principle of the kinetic interaction of microparticles in a solution where the drug content of the urine is directly proportional to the inhibition of the microparticle aggregation.	• May be used to test a wide variety of drugs of abuse.	• Cross-reacts with some OTC preparations when testing for amphetamines.

Sources: Armbruster, Hubster, Kaufman, & Ramon (1995); Center for Substance Abuse Treatment (2006b); Neerman (2006); Verebey, Meenan, & Buchan (2005); Vidal & Skripuletz (2007).

Appendix C—Laboratory Confirmatory Drug-Testing Methods

Testing Method	Description
Gas Chromatography (GC)	• A technique for separating and analyzing compounds that can be vaporized without chemicals.
High-Performance Liquid Chromatography (LC)	• A chromatographic technique for separating and analyzing chemical substances in solution. • Separation is based on absorption, partition, ion exchange, and/or size exclusion.
GC/Mass Spectrometry (GC/MS)	• A combined technique coupling an MS (mass spectrometer or mass selective detector) with a GC instrument. • After the GC has separated the analytes in a specimen, the components enter the MS, which identifies and quantifies the separated analytes. • The MS creates charged particles (ions) and separates them according to their mass-to-charge ratio. • The ions form unique mass spectra, which are used to identify analytes. • Most common method of confirmation.
GC With Tandem MS (GC/MS/MS)	• The same principles, as described above. • The MS produces and isolates the ion of interest, which is then reacted with a reagent gas to produce fragments. • The MS scans the fragments (called the "productions") to obtain structural information. • This method is more sensitive than GC/MS.
LC With MS (LC/MS)	• LC can accommodate nonvolatile compounds. • Separation is based on distribution of the solutes between a liquid mobile phase and a stationary phase. • MS phase is the same as described above. • Widely used for pain management.
LC With Tandem MS (LC/MS/MS)	• Described above, with two MS phases. • Also used in pain management.

Appendix D—Laboratory Specimen Validity-Testing Methods

Testing Method	Analytes	Description
Colorimetry	Specific gravity, pH, creatinine, adulterants (general or specific tests)	• A technique that compares the color developed in a solution of a test material with that in a standard solution, quantitated on the basis of the absorption of light. • The concentration of the analyte is determined by visually noting the color or electronically measuring the intensity of light at selected wavelengths (i.e., spectrophotometry).
Refractometry	Urine-specific gravity	• A method for determining the amount of solute (i.e., urinary total solids) in the urine by measuring the index of refraction. • A urine specific gravity refractometer displays specific gravity values converted from refractive indices.
Potentiometry	pH	• An instrument (e.g., pH meter) that measures hydronium ion activity and converts it into the negative logarithm (base 10), which is the displayed pH.
Atomic Absorption Spectrophotometry	Adulterants	• A method in which the specimen atoms in the vapor phase absorb ultraviolet or visible light and transition to higher electronic energy levels. • The analyte concentration is determined from the amount of absorption of specific wavelengths.
Capillary Electrophoresis (CE)	Adulterants	• A technique based on the mobility of ions in an electric field. • Positively charged ions migrate toward a negative electrode, and negatively charged ions migrate toward a positive electrode. • Ions have different migration rates depending on their total charge, size, and shape and can therefore be separated. • CE is an electrophoretic method using a small-bore, fused silica capillary tube.
Gas Chromatography/ Mass Spectrometry (GC/MS)	Adulterants	• Full-scan MS or selected ion monitoring identifies unknown analytes. • The identification of the analyte of interest relies on a comparison with the mass spectra of an analyzed reference standard or reference library spectra.
Inductively Coupled Plasma/MS	Adulterants	• A combined analytical method in which a vaporized sample is introduced into a radio frequency-induced plasma, is ionized, and then enters an MS for identification and quantification.

Testing Method	Analytes	Description
Multi-Wavelength Spectrometry	Adulterants	• A method that uses multiple wavelengths of light (or other electronic transmissions) to identify an analyte. • The method generates corrected absorbance values that are related to the analyte concentration.
Ion Chromatography	Adulterants	• A form of liquid chromatography that uses ion-exchange resins to separate atomic or molecular ions based on their interaction with the resin.

Appendix E—Glossary

Adulterated specimen. A specimen containing either a substance that is not a normal constituent for that type of specimen or containing an endogenous substance at a concentration that is not a normal physiological concentration.

Adulteration panel. Testing a specimen for substances that mask the presence of illegal drugs in that specimen.

Aliquot. A fractional part of a specimen.

Analyte. Any material or substance subjected to analysis (testing).

Chain of custody. Procedures to account for the integrity of each specimen or aliquot by tracking its handling and storage from point of specimen collection to final disposition of the specimen and its aliquots.

Concentration. Amount of a drug in a unit volume of biological fluid expressed as weight/volume. Urine concentrations are usually expressed as nanograms per milliliter (ng/mL), micrograms per milliliter (ug/mL), or milligrams per liter (mg/L).

Confirmatory drug test. A second analytical procedure performed on a different aliquot of the original specimen to identify and quantify the presence of a specific drug or drug metabolite.

Confirmatory validity test. A second test performed on a different aliquot of the original specimen to support or deny the initial validity test result.

Conjugate. A compound produced by the chemical joining of at least two other compounds.

Creatinine. An endogenous substance appearing in the urine, commonly used to estimate kidney functioning.

Cutoff concentration or level. The measurement used to establish and report a specimen as negative or positive.

Deconjugate. The breaking down of a substance into the original compounds.

Dilute specimen. A urine specimen whose creatinine is less than 20.0 mg/dL, but equal to or greater than 2.0 mg/dL and whose specific gravity is less than 1.0030, but equal to or greater than 1.0010.

Diversion (of prescribed medications). The act of selling or giving away prescribed medications instead of taking them as prescribed.

Initial drug test. A test to differentiate a negative specimen from one that requires further testing for drugs or drug metabolites. Also called a screening test.

Invalid result. The result reported when a scientifically supportable analytical test result cannot be established for a specimen.

Matrix. The biological medium tested for the presence of drugs or drug metabolites.

Medical Review Officer (MRO). A licensed physician who reviews, verifies, and reports a specimen test result in regulated workplace programs.

Metabolite. A compound produced by enzymatic or chemical means while in the body, usually to a more water soluble form for easy excretion.

Negative test result. The result reported by a laboratory when a specimen contains a drug or drug metabolite less than a prespecified cutoff level or concentration.

Pharmacogenomic. The genetic factors that influence an organism's response to or metabolism of a drug or a medication.

Point-of-care test (POCT). A drug or validity test conducted at the collection site to obtain an initial or screening result on whether a specimen contains a drug or drug metabolite or is not a valid specimen. Also called onsite, point-of-service, or point-of-collection test.

Positive test result. The result reported by a laboratory when a specimen contains a drug or drug metabolite greater than or equal to a prespecified cutoff level or concentration.

Sample. A representative portion of a specimen or quality control material used for testing.

Specimen. Fluid or tissue derived from the body collected for testing.

Substituted specimen. A specimen that has been submitted in place of the patient's urine, either as evidenced by creatinine and specific gravity values that are outside the physiologically producible ranges of human urine or is another person's urine.

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