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Review and Recommendations for Drug Testing in Substance Use Treatment Contexts

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Introduction

Drug use implications and the role of testing

Drug and alcohol use have been associated with substantial impairments in functioning in a number of settings including driving [1], the work place [2], family functioning [3] and military service [4, 5]. In the United States alone it is estimated that 24.6 million Americans over the age of 12 are current illicit drug users while approximately 137 million Americans are current alcohol consumers [6]. Given the association of drug use with negative outcomes and behaviors including depression [7, 8], criminal offending [9-11], sexual risk [8, 12], poor parenting [13] and cardiovascular disease and death [14, 15], it is important for health practitioners to be able to appropriately identify and, when appropriate, treat problematic substance use. It is within this framework that drug testing methods (DTM) have been used as a detection tool in settings such as the workplace, military, athletics, criminal justice system, health care settings, and drug treatment facilities [16-18]. Drug testing is a complex process that requires a thorough understanding of the substance use process as well as the metabolic processes involved in the absorption, distribution, metabolism and elimination of the used substances. For example, drug testing approaches can vary in terms of the specimen (e.g., urine, blood, hair, sweat, and saliva), substances tested for, the identification time-frame and specificity, the cost of the analysis, frequency of required testing, invasiveness of the drug test, sampling strategy (ex. Random sampling or all subjects are tested), the extent of testing feedback offered to patients, and consequences of positive findings [19]. Additionally, self-report methods as well as physiological testing may be used to screen for drugs. Since drug use may be underreported on a self-report basis, biological testing may be necessary for confirmation purposes [18, 20]. Additionally, drug testing is often used to assess medication compliance within clinical settings that take advantage of medication assisted treatment (MAT). Research has shown that evaluating patient compliance using testing methods can be an important tool with potential for improving outcomes in treatment [21].

Current paucity of standards

Given the importance of drug testing in the prevention, detection and treatment of substance use problems, it is somewhat surprising that few accepted standards regarding the application of testing methods seems to currently exist [22]. The clearest set of standards that exist regarding drug testing are found in the federal government's employment-related drug-testing [23]. The same standards are loosely found in non-governmental employment-based testing although variations are found in these setting as well. Within the mental health and substance use disorder (SUD) treatment field, little is standard when it comes to drug-testing aside from the fact that urine testing is the most commonly utilized testing method. For instance, while some SUD treatment facilities utilize

randomized comprehensive urine drug testing other providers use regular testing intervals for alcohol alone with urine analysis utilized only when suspicion of use is present. Such variability in testing practices can lead to variable detection rates and therefore variable levels of testing effectiveness resulting in unpredictable reliability of testing methods and practices. It is our belief that the establishment of clear guidelines regarding drug testing within the mental health and SUD treatment contexts would help standardize the practice and therefore allow for more consistent application and interpretation of results.

Impact of Testing on Treatment Outcome

Little research has been conducted to assess the impact of drug testing on actual outcomes in substance abuse treatment. A French study conducted by Dupouy [24] evaluated the effectiveness of drug testing for treatment retention in an outpatient setting involving opiates. In France, there are guidelines for addiction care and it is advised to have standardized screening tests throughout treatment. In this particular study, tests were completed using automated analyzers in the laboratory or by using drug screening kits. These tests are reimbursed by the French health insurance system with no limit on their number or time period. This cost elimination relieves the burden of drug testing on both the facility and those in treatment and similar methods to achieve this cost elimination may play a vital role in improving treatment [24]. Dupouy's [24] study in the outpatient setting found that there was significantly improved treatment retention through the use of drug testing. The possible reasons for this higher retention rate includes the hypothesis that patients who agree to drug testing may be more compliant patients in general and may be self-selected on their motivation. In another study, researchers witnessed a reduction in drug-related friendships between a cohort of individuals as a consequence of instituting urine screens at randomized intervals [25]. In another hypothesis, it was evaluated that tested patients may more often be those who have heavier addiction problems and thus, may have a higher need to be evaluated for their drug consumption. This improvement in retention rates may also be contributed to better assessment of drug consumption that helps practitioners better communicate with their patients. By eliminating the potential of false information about drug use by patients, practitioners can better assess what should be done to help each individual if they are still facing difficulties of abstinence during treatment [24]. The idea of modifying treatment based on whether the individual is still abusing or not creates a dynamic mode of treatment that better adjusts to the hurdles of drug treatment. Though, because in some situations the cost of routine testing accumulates quickly, clinicians must be proactive in adjusting treatment procedures in response to drug screening and eliminate excessive or redundant testing [26]. Offering tools such as counseling that focused on problem- solving, cognitive restructuring, and functional analysis helps individuals deal with their relapse in a beneficial manner [27]. When accounting for cost and adjusting treatment concurrently, drug testing analysis will ultimately help improve treatment for patients.

As mentioned earlier, drug testing occurs within numerous settings. While this paper will focus mostly on SUD treatment settings, we believe that much of the information contained within this work applies across settings. However, the different requirements and regulations applicable within many of these setting would suggest that additional future work should focus on recommendations specific to these contexts.

Methods and Existing Standards

Types of tests

Urine

Urine is the most common specimen analyzed in drug testing because of the ease of collection and high concentrations of drugs and metabolites found in urine [16]. The three methods of urinalysis include thin layer chromatography (least sensitive and least expensive), enzyme/immunoassay and radioimmunoassay (more expensive and more sensitive), and Liquid chromatography (most expensive and most reliable). Immunoassay techniques can be divided into laboratory based or point-of-collection (POC). There are several types of immunoassay techniques including enzyme-multiplied immunoassay technique (EMIT; a form of enzyme immunoassay), fluorescence polarization immunoassay (FPIA), immunoturbidimetric assay, and radioimmunoassay (RIA) [16]. The standard in drug testing is to complete an immunoassay screen and, upon a positive initial screen, to conduct a Liquid chromatography/mass spectrometry (LC-MS) as a confirmation [16]. Completing a confirmatory analysis is important to reduce false-positive screens, which may result from cross reactivity, and may negatively impact the tested individual. Cross reactivity may occur if an over-the-counter drug or a common environmental chemical shares common chemical properties with the target drug and therefore influences the results [18]. It is important to note that screening tests may not be able to differentiate between different drugs in the same drug-class or between different drugs that have common metabolites. Validity tests should be performed in order to determine if the urine sample has been diluted, substituted, or tampered with [28].

Detection window: Urine analysis offers an intermediate window of detection period that may depend on the method of using the drug. For example, when a drug is inhaled or smoked the drug is almost immediately incorporated into the body's systems and is quickly excreted from the body. Conversely, when the drug is ingested orally, absorption is slower and excretion is slower as well. In general, a urine specimen will have the highest concentration of the parent drug and metabolites 6 hours after ingestion of the drug, and the majority of the drug will be excreted after 48 hours. However, if a large quantity of the substance has been consumed, the detection period may be extended due to the drug's accumulation in the body.

Special considerations: Temperature and appearance of the urine sample should be noted to maximize validity and reduce the possibility of tampering. Urine that is not in the range of 32 - 38 °C or urine that looks very soapy should be considered to be an altered specimen or replacement substance. Urinary creatinine should also be recorded and creatinine

levels lower than 20 mg/dl may suggest an altered specimen or the addition of another substance [28]. The donor of the urine specimen may require supervision at the time of collection if sample tampering is suspected. Additionally, a urine screen should not be utilized as a sole diagnostic measure, it is a tool which may strengthen and support a diagnostic claim but should not be held as infallible marker; clinical and professional judgment and context should always be presented in tandem with findings [29].

Advantages and disadvantages: Advantages of urinary analysis include the ability to collect sufficient quantities to allow for retesting when needed, the availability of high concentrations of parent drugs and metabolites making lab testing easier, and the availability of point-of-collection tests making onsite screening easier. Some disadvantages include a shorter detection period when compared to hair analysis, relatively easy specimen tampering, the high expense of reliable and valid onsite testing, and the invasive nature of testing when supervising the donor during collection [28]. Another disadvantage is the ambiguous nature of the utility of a urinary screen. Dupouy and her colleagues [30], conducted a literature review assessing the benefits of utilizing drug screens to manage patients. They concluded that there was no substantial evidence to warrant the use of drug screens to manage patients. As such and in line with findings from Tenenbein [29], testing should be conducted with well and clearly defined goals not because of routine protocol.

Cost: Urine analyses completed in the clinical setting vary in price depending on the number of drugs tested for. A 5-Panel Testing Cup (tests for 5 different drugs) costs approximately $4. A 14 Panel Testing Cup (tests for 14 different drugs) costs approximately $7. Another common urine drug testing technique is testing with Dip Cards, a drug-screening test that is dipped into a urine receptacle. A Single Panel Dip Card costs about $2 while a 12-Panel Dip Card costs approximately $6 [31]. Urine Samples sent to a laboratory vary in cost depending on the amount of drugs being tested for and the lab performing the testing. Screening tests range from $69 to $148 and confirmatory tests sent to a lab to be analyzed, range from $92 to $165 dollars [32].

Oral

Oral fluid analysis is a new technology and is relatively expensive but non-invasive and easy to collect [18]. This drug testing method can be used in the workplace, to test driving impairment, in legal issues, as a diagnostic tool, and to determine detection times and pharmacokinetics of drugs [33]. Saliva testing is generally seen as a complimentary method to other testing methods, such as urinary analysis and blood due to its shorter detection window and relative novelty.

Detection window: Oral fluid testing can detect drug use approximately 12-24 hours after drug ingestion [33]. This makes saliva analysis a useful tool for detecting recent drug use. In addition, the parent drug is usually present in high concentrations, making oral fluid testing great for identifying drugs. However, as with other tests, drug concentration levels found in saliva may fluctuate based on the individuals physiology, the type of technique used to collect the fluid, and other external/environmental factors [33-35]. Due to the high concentrations of the parent drug in oral samples, the cut off values are larger in oral devices compared to GC/MS and vary from substance to substance, for example, cocaine metabolites: 4 ng/mL (GC/MS) v. 20 ng/mL (oral); THC metabolites: 0.2 ng/mL (GC/MS) v. 40 ng/mL (oral) [35].

Special considerations: Collecting saliva can be done in several ways. Expectoration provides a robust specimen, but it tends to be contaminated with food and other debris and may be difficult to work with in the laboratory due to its viscous nature. Other collecting methods include using an absorbent pad to collect oral fluid, which can then be added to a diluent; the diluent is used in the drug analysis. It takes approximately 1-3 minutes to collect saliva using an absorbent pad. Another method, Drug Wipe can be used to just wipe the tongue or skin, and only takes a few seconds to complete. Unfortunately, this method collects a small amount of saliva making it near impossible to complete a confirmatory analysis [36]. Using citric acid candy, chewing gum, or other agents can stimulate oral fluid, but this will change the properties of the drug in the saliva such as the pH and concentration. Some drugs themselves may affect the amount of saliva produced. Studies have shown that some collection devices are better suited for certain drugs. For example, the device Salivette is a poor device to use for THC, but great for codeine, whereas the Cozart collector is great for THC [37]. A possible difficulty in collecting saliva, a person may exhibit dry mouth syndrome because of anxiety of the collection process or dehydration. This makes collection time longer and may take several minutes to collect 1 ml of saliva [33].

Advantages and disadvantages: In recent years, many point-of-collection devices have been created for testing saliva. These devices include an oral collection apparatus and technology to detect different drug classes. Examples of these devices are the Cozart RapiScan, Securtect Drug Wipe, Drager Drug test, and Brana Oratect. Although these devices may be useful, it is important to consider that they may have different specifications and therefore may have different consistencies, efficiencies, and sensitivities. This may make results across devices inconsistent and difficult to interpret. For laboratory testing, there are many enzyme-linked immunosorbent assay (ELISA) immunoassays available. These methods of screening are considered reliable in testing oral fluids. As for most specimens, a confirmatory analysis using LC-MS should be conducted after initial screening [33, 37].

While collecting saliva, a testing-representative can completely observe the process, making adulterating or substitution of specimen difficult. However, as discussed, there are still factors that can affect the drug concentrations in saliva and need to be considered. A study conducted using one specific device, Oratect, showed that drug concentrations were not affected by foods, toothpaste, and beverages 30 min after exposure [35].

Hair analysis

Over the past 20 years, drug testing by hair analysis has become more popular and the method can be an important complimentary technique to other forms of drug testing in both

clinical and forensic toxicology [38]. An important to aspect to administering the appropriate substance abuse treatment is to obtain accurate accounts of an individual's drug use history, yet self-reports are often plague with underreporting of drug use [39]. Hair testing allows for a wider window of detection and quantification not possible through traditional means such as urinary analysis as well as validating patient self-reports [40].

Hair samples can be analyzed using immunological or chromatographic techniques. Cooper et al. [38] recommend that laboratories use sensitive enough immunoassay techniques to detect low concentration levels of the drug, as hair samples contain lower drug levels than urine or blood. If laboratories use immunoassay-screening methods, they must also conduct a confirmation test, such as LC-MS. The confirmation tests should also be sensitive enough to detect low drug concentration levels. In general, drug concentration levels tend to decrease from the root to the end of the hair strand.

Detection window: Hair analysis allows for the detection of drugs even months after the initial use [41], depending on the length of hair available at collection. This makes hair testing useful in situations where information is needed regarding the chronicity of the drug use or if a long period of time has passed since the drug use [38]. In addition, hair testing is sensitive enough to detect drug use after a single exposure. While hair testing is a sensitive method with a long detection window, it has been suggested that this method has difficulty detecting drug use within the last 7 days [18], reducing its utility for ongoing substance use detection within SUD treatment contexts.

Special considerations: Drugs are absorbed into the hair shaft through capillaries located at the hair root and the hair shaft itself absorbs sebaceous and sweat gland secretions that may carry drugs and metabolites [18, 42]. In addition, hair strands may absorb other drugs or substances present in the external environment [43]. Once drugs are absorbed into the hair shaft, their concentration levels may be affected by differences in hair structure, porosity, hair growth [44], melanin content [45, 46] and may be affected by chemical hair treatments [18, 47-49]. The consideration of all these factors and their impact on drug concentration levels is important when analyzing the results of hair analysis.

Before actual testing, hair samples should be washed to remove any possible contaminants including cosmetic products, sebum, sweat, skin cells, lice, bodily fluids, or other external contaminants. Therefore, it is important that laboratories have good hair sample washing procedures and Cooper et al. [38] recommend washing hair samples with organic solvents and aqueous solutions. It is important to consider that drug concentrations may be reduced during washing, and therefore too much washing may do more harm than good. After washing and drying, the hair sample should appear homogenous and be ready for incubation and extraction. When conducting extractions, it is important to tailor extraction solvents according to the target drugs being extracted. Some extraction solvents may react with or affect the drug being extracted. Finally, Cooper et al. [38] recommends that laboratories conducting hair analyses should join external proficiency programs to evaluate their hair testing methods [38].

Advantages and disadvantages: Some suggest that collecting hair specimens is less invasive than collecting a urine sample [38], especially when said urine collection requires observing the client, which is uncomfortable and can be embarrassing for both the donor and observer.

While head hair is preferred, if collecting head hair is not possible then alternative sites may be used such as pubic hair, underarm hair, and beard hair. It is important to consider that collecting hair from intimate sites may be intrusive and uncomfortable for the donor, therefore making this procedure more invasive.

Sweat

Sweat testing utilizes transdermal patches comprised of a membrane that is permeable to water, oxygen, and carbon dioxide while capturing any ingested drugs and their metabolites may be used to detect drug use [50]. Certain drugs and metabolites are transported to the surface of the skin through passive diffusion from blood vessels to sweat glands and are then excreted. After the accumulation period is over, usually one to fourteen days, the patch is removed; the analytes are washed off the patch with a proper organic solvent (i.e. methanol) and analyzed using such tests as LC-MS/MS and GC/MS tests [18].

Special considerations: One such example of a sweat patch being used today by clinicians is the PharmChek™, a patch that was well tolerated for seven days by participants [51]. While testing various chemical agents on the patch by injecting them into or directly under the patch while being worn, it was found that chemicals such as tile-cleaner and detergents could lead to false-positives in the immunoassay analysis of the sweat patch analytes while Visine™ eye drops and Ben Gray ointment cause false-negatives in the same tests [18].

Advantages and disadvantages: In addition to the reduction in cost of utilizing this method of testing compared to urinary analysis, sweat patches are advantageous as a way of drug testing because of the non-invasive nature of the patches, with patients reporting this method as being less embarrassing than other methods of testing [18]. The patches are tamper resistant so if the client tries to remove the patch at any point, a clinician should be able to easy identify the patch had been tampered with. However, during the somewhat extended period the patch is worn, there is some risk of either accidental or purposeful removal of the patch [18]. One major disadvantage relates to the small amounts of analytes that are collected on the patch when compared to other collection methods such as urine and blood, which complicates the process of testing and re-testing for confirmatory purposes. Finally, the length of time the patches are worn do not allow for immediate screening results, unlike urine and saliva testing, which can reduce the utility of sweat for clients participating in ongoing treatment.

Cost: Sweat testing is a relatively cheap alternative to urine testing. While urine tests must be conducted multiple

times a week, the use of a sweat patch reduces the amount of drug testing that needs to be conducted as it is a cumulative method of drug testing. The typical cost of such testing is $10 per drug for on-site testing, $35 for an initial screening test of the substances collected on the patch, and $65 for any additional screening to confirm the presence of specific drugs and rule out false positives. In addition, little training is required in order to administer the patch to any potential client.

Breathalyzer

Historically, breathalyzers have been used exclusively in legal and law enforcement settings, by which the police utilize the technology in order to accurately determine an individual's level of intoxication in relation to driving offenses. However, a large body of evidence has refuted their clinical utility largely due to the inefficient legislation and regulation surrounding their use and their association with illicit activities [52]. These tools have seen a boost in psychiatric and health environments where breathalyzers are able to quickly assess an individual's level of blood alcohol concentration (BAC). This information allows professionals to accurately and effectively administer appropriate treatment and as such has recently gained favor as an important tool in alcohol treatment settings [53]. However, the accuracy and reliability of breathalyzers must first be considered to understand their utility in clinical settings.

Detection window: Breathalyzers, currently limited to the detection of alcohol, can identify Blood Alcohol Content (BAC) between 20 minutes and 3 hours of ingestion. Differences in detection window can depend on alcohol concentration, alcohol metabolism and individual variables such as weight and gender.

Special considerations: The majority of breathalyzers implement either fuel cell sensor technology or semiconductor oxide sensor technology to measure the blood alcohol content (BAC) in an individual's blood. Semiconductor oxide sensors use a tin-oxide substance to measure BAC. While the lower power requirements and cost of manufacturing of the semiconductor sensor results in a smaller, more affordable device, they are often thought to be less reliable compared to their fuel cell sensor counterparts [54]. Chemicals, mainly environmental pollutants, have been discovered to effect BAC accuracy in semiconductor sensor readings. Semiconductor sensors are also sensitive to acetone secretions, providing a higher probability of a false positive when testing an individual with diabetes. Whereas fuel cell breathalyzers are targeted towards professionals and organizations requiring a device that can handle higher test volumes, semiconductor sensors are primarily marketed towards personal consumer use and should not be considered sufficiently reliable for clinical settings.

Breathalyzers with fuel cell sensors offer high accuracy and sensitivity, and employ the same advanced fuel cell technology that is used by law enforcement for roadside alcohol testing, as well as in substance abuse centers, clinics, and businesses [54]. Fuel cell sensors rely on an electrochemical process that oxidizes the alcohol in a breath sample. The oxidization produces an electrical current that the breathalyzer measures to determine the BAC. The strength of the current corresponds to the volume of alcohol present in the sample. Breathalyzers employing fuel cell technology are engineered to offer accurate, long-term reliability over a comprehensive range of blood alcohol concentrations.

Advantages and disadvantages: A primary disadvantage of breathalyzers, especially older models, is their tendency to provide false negatives by incorrectly identifying other substances, similar in molecular structure or reactivity to ethanol. A positive test result can be misleading because it can be positive from extraneous exposure to alcohol from any of a myriad of products such as food, mouthwash, or over-the-counter medications [55, 56]. Retesting can be an important procedure as a short waiting period and an additional test can, for the most part, resolve the inconsistency.

However, mistakes from instrument errors have been reported. The alcohol sensor is highly sensitive and will not function correctly when wet or damaged. Its response can also be affected by temperature and humidity. Therefore, a margin of error is ever-present and must be considered [52]. The breathalyzer must be kept at room temperature in a clean, dry place and consistent calibration of the unit against standards is paramount. The most precise BAC can only be acquired from measurements of blood.

Blood

Like sweat, hair and urinary analysis, blood testing allows another way for researchers and clinicians to monitor clients yet, due to the short time many substances are detectable in the blood, this method may not be the optimum method of testing in all situations. Blood analysis and detection of analytes is conducted under the power of mass spectrometry (MS) in conjunction with either liquid chromatograph (LC-MS) [57].

Blood testing is a powerful tool rooted in forensic toxicology for cases of criminal investigations but with the growth and accessibility of mass spectrometry in smaller labs it is easier for clinical and research professionals to perform blood assays on clients to gain a clearer understanding of drug use and habits [57].

Detection window: Blood testing provides a relatively short testing windows of approximately 1-8 hours [58, 59]. Opiates, due to short half-lives (between 2.5 and 5 hours), hydromorphone, hydrocodone, and oxycodone quickly disappear from blood, making opiate detection through blood samples more difficult. It is presumed that the half-life of oxymorphone is also quite short [60].

Cost: Cost of testing varies depending on lab and level of insurance client has.

Advantages and disadvantages: Blood testing is considered one of the most invasive testing methods and requires a clean, and preferably sterile, testing environment [61]. This requirement alone can be considered a major disadvantage of blood testing methods and render them impractical for most treatment contexts. Additionally, in order to be performed appropriately, staff trained in phlebotomy is typically required for the performance of blood-draws. This again limits the utility of this method in many clinical, non-hospital contexts. Finally, the cooling and storage requirements

for blood are more stringent than those of either urine or saliva, further complicating the use of this method in non-hospital treatment settings.

Current Best Practices

As mentioned earlier, there is currently no one agreed-upon standard procedure for drug testing throughout the SUD treatment system despite the global prevalence of SUD treatment centers. Although there are overarching trends, large variability can be found in the type of drug testing, frequency and application methods. This section will focus on drug testing standards that exist in other settings, specifically the federal government's employment standards and the Substance Abuse and Mental Health Services Administration's primary care guidelines, which will provide insight into possible standards to be applied in other settings.

Federal

All federal agencies in the United States must follow certain drug-testing guidelines provided by the Substance Abuse and Mental Health Administration. In the federal workplace, a urinary analysis can be conducted that tests for amphetamines, cannabinoids, cocaine, opiates and phencyclidine, often referred to as the SAMHSA-5 [28]. However, if it is a federal agency, the drug test but must be reviewed by a Medical Review Officer (MRO). Private, non-unionized workplaces can drug test, but do not have to follow SAMHSA's instructions. Because of privacy laws, most workplace drug tests do not include drug testing of prescription drugs as this could be considered an invasion of privacy. However, when drug testing for therapeutic reasons, testing for prescription drugs is important to assess both for abuse and medication adherence [62].

In the 1970's the U.S. Federal Government created a program to oversee drug testing laboratories The Federal Government mandated that Substance Use Disorder (SUD) treatment centers drug test during initial assessment and then as a preventative screen, as a part of the treatment plan, and as a way to observe the patient's use of illegal substances and the obedience to pharmacotherapy treatment [28]. The Federal Mandatory Workplace Guidelines for the cutoff concentrations of drugs is often used as a guide for SUD treatment centers and they are as follows: 50 ng/mL for marijuana metabolites, 150 ng/mL for cocaine metabolites, 2,000 ng/mL for opiate metabolites, 10 ng/mL for 6-Acetylmorphine, 500 ng/mL Amphetamines, 25 ng/mL for Phencyclidine, and 50 ng/mL for Methylenedioxymethamphetamine [28]. However, the cutoffs may need to be altered in order to best fit the needs of the patients and the treatment being offered [23]. The Mandatory Federal Workplace Guidelines require a urine sample of 30 mL. This may not be enough if the sample is positive for multiple drugs, which is often the case in some addiction treatment centers, so a second specimen may be needed [23].

Private setting

Private addiction treatment centers have the ability to use any kind of drug test they want with any frequency, but once again, they are limited by cost and time. One of the major issues is insurance. The type and amount of drug testing that occurs will depend on the patient's insurance or the ability of the patient to afford the costs of the drug tests [63]. However, if expense is not an issue, then various drug testing techniques could be utilized. Urine is the most widely used drug-testing technique because it can test for many different types of drugs on test panels and has a window of detection of 1 to 3 days. However, the more analytes requested, the more expensive the test usually is. Oral fluid drug tests are also becoming more common, but that have a somewhat shorter window of detection ranging from 12 to 48 hours. Hair and nail testing are used the least because they are the most expensive as well as the most invasive, but they can detect drug use for up to 90 days [28]. Private addiction treatment centers have a large amount of flexibility with their drug testing procedures; however, they are limited by cost, time, and insurance so they often end up following the SAMHSA drug testing guidelines.

Drugs of Abuse

Alcohol

Prevalence and route of administration

Alcohol use in individuals aged 12 or older in 2014 is estimated at 139.7 million users, corresponding to roughly 52.7% of the U.S. population over the age of twelve. Additionally, an estimated 60.9 million Americans are current binge drinkers with 16.3 million engaging in heavy alcohol use, defined as having five drinks or more on five or more days in the past month [64]. Testing and identifying the presence of alcohol through its various metabolites is important in substance use disorder (SUD) treatment settings as approximately 79% or 17 million of those struggling with SUD report alcohol as a primary or secondary substance of abuse [64]. The testing of alcohol use may be conducted through all traditional testing methods (e.g. hair, urine, sweat, breath or blood), although some settings may make the use of certain methods preferable over others.

Metabolites

The majority (>95%) of ethanol that is consumed is converted by alcohol dehydrogenase into acetaldehyde which in turn is processed into acetic acid [65, 66]. An estimated four to five percent of ethanol in its original unprocessed form is typically excreted through sweat, urine, and breath. A remaining trace amount is converted by two different metabolic processes to form ethyl glucuronide (EtG) and ethyl sulfate (EtS) [65].

Testing window

The use of EtG, EtS, and ethanol as reliable and valid markers for alcohol has been established though numerous studies [57, 65, 67]. However, the establishment of the most valid cutoff points and the establishment of specific detection windows for each of these markers is still being debated. Recent research identified metabolite duration for EtG and EtS detectable up to 48 hours with 500 ng/ml & 250 ng/ml cutoff rates respectively [57], in direct contrast to industry standards,

which suggest that EtG and EtS markers are observable for up to 80 hours. Ethanol is reported to remain detectable for about two to six hours after alcohol consumption before being metabolized [65].

Extraneous exposure

High concentration cutoffs are recommended for commercial testing to eliminate the risk of false positives through extraneous and incidental exposure, although increasing cutoff values will invariably reduce the ability to detect sporadic and minimal alcohol use [57]. Jatlow et al. [57] also note the possibility of EtOH detection even without alcohol consumption, for example incidental exposure through the excessive use of hand sanitizer. In the case of hair testing, some over the counter hair care products contain EtG and may result in false positive reports [68].

Special consideration

Breathalyzer monitoring, especially using remote, cellular photo digital breathalyzers (CPDBs), has been shown to be a substantially more reliable, and valid, tool for assessing alcohol use in outpatient settings [53] when compared to EtG testing. Specifically, among 12 social drinkers, CPBDs were able to detect 98.8% of self-reported drinking episodes while random EtG tests detected 1.8% of self-reported drinking episodes.

Marijuana

Prevalence and route of administration

According to the results of the 2013 National Survey on Drug Use and Health (NSDUH) conducted by SAMHSA, 19.8 million people (6% of the population) were current users of cannabis. Cannabis use was most common among respondents aged 18 to 25, and cannabis was more prevalent in males as compared to females [69]. Due to its common use and ease of detectability, research regarding THC detection in users via blood, urine, hair, nail, and saliva analyses is robust and widely available.

Metabolites

Marijuana, or cannabis, refers to the dried leaves, stems, flowers, and seeds from the plant Cannabis Sativa. Cannabis is usually smoked in its dry plant form, in a concentrated resin called hashish or in a liquid form called hash oil [69]. THC is the primary psychoactive ingredient in cannabis. The major metabolites of THC are 11-hydroxy Δ^9_Tetra hydrocannabinol (11-OH-THC) and 11-nor-9-carboxy-Δ^9-tetrahydrocannbinol (THCCOOH). In urine, approximately 20% of consumed cannabis is excreted, with the primary metabolite present being THCCOOH [70]. THCCOOH reaches peak levels in the body three hours after the individual has smoked and is detected in both urine and blood by the presence of its glucuronide conjugate form after being reacted with glucuronic acid. 11-OH-THC is the predominant metabolite found in feces and has been found at higher concentrations in samples after ingestion rather than inhalation [71].

Testing window

The detection window for THC is highly variable based on a number of factors including dosage, frequency of use, time since last use, and metabolism of the individual being tested. The biological half-life of THC is 1.3 days for infrequent users and five (5) to thirteen (13) days for chronic users, depending on frequency of use. THC and its metabolites are lipid soluble and thus accumulate in fatty lipid tissues, therefore individuals with higher body mass generally have a larger detection window [16]. For blood tests, the detection window is twelve (12) to twenty-four (24) hours and thus this method is better used for detecting recent use. For urinalysis, the detection window is one (1) to seven (7+) days, with a cutoff concentration of 50 ng/mL [70]. For hair and nail analyses, the detection window is up to 90 days and is thus more likely to detect past and regular use. The detection window for saliva testing is only four (4) to six (6) hours and there has been debate over the validity of this kind of testing, therefore it is less commonly used.

Extraneous exposure

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to cause false-positives in urine screening for THC possibly due to interference with an enzyme involved in the EMIT test. False-positives have also been reported after the use of proton pump inhibitors (PPIs) and the non-nucleoside reverse transcriptase inhibitor (NNRTI) Efavirenz that is commonly used in the treatment of HIV. Studies have concluded that passive or second-hand exposure to marijuana smoke as well as consumption of hemp-seed tea do not cause false positives because even trace amounts of THC found in urine do not meet the cutoff concentration for EMIT or LC-MS tests [16].

Special considerations

Due to the high prevalence of cannabis use and the subsequent high testing rate, clinicians should remain vigilant and aware when testing clients. Eye drops containing the chemicals benzalkonium chloride and borate buffer have shown to decrease the concentration of 9-carboxy-THC in urine without altering the antibodies involved in immunoassay and can thus cause false-negatives in urine tests, however these ingredients do not chemically alter 9-carboxy-THC, still making it detectable by LC-MS [16].

Sedatives

Prevalence and route of administration

Benzodiazepines and Z-drugs such as Ambien and Lunesta are sedative hypnotics prescribed to help patients suffering from insomnia, anxiety, convulsive disorder, acute behavioral disturbances, as well as to treat withdrawal from alcohol and cocaine [71, 72]. Long term use of sedatives can lead to drug abuse and dependence even among individuals who are appropriately prescribed these medications. Benzodiazepines can be administered intravenously, orally in forms of pills, and less commonly using nasal devices [73]. Across North America and Europe, the prevalence of long-term use of sedatives, ranges from 0.4-6% of the population with higher rates seen in patients older than 65. In the US alone, sedative use has reached upwards of 20% prevalence [71, 74]. Testing for sedatives can be conducted using hair, nail, urine, saliva and blood collection methods [75-78].

Metabolites

Benzodiazepines affect the central nervous system (CNS) by promoting the binding of the neurotransmitter (gamma)-aminobutyric acid (GABA) to the $GABA_A$ subtype of GABA receptors in the CNS. Once in the body, benzodiazepines are extensively metabolized. For example, Diazepam is broken down into nordiazepam, oxazepam, and temazepam, and Chlordiazepoxide is broken down into nordiazepam and oxazepam. These metabolites are detected in drug tests and can assist in identifying the original target drug. The metabolites of different benzodiazepines depend on the original target drug. For example, Alprozolam is detected by the presence of alpha-hydroxyalprazolam, Triazolam detected as alpha-hydroxytriazolam, Clonazepam detected as 7-aminoclonazepam, while the presence of Flunitrazepam is marked by 7-aminoflunitrazepam and Flurazepam by hydroxyethyl-flurazepam [79].

Testing window

The detection window for benzodiazepines can range from 2-10 days depending on whether the specific drug is a long- or short-acting benzodiazepine with longer-acting drugs having longer detection windows [16].

Special consideration

It is important to consider that urinary analysis will not be able to detect between pharmacological use and substance abuse [16]. Furthermore, assays will not distinguish between single use and long-term use. Also, cross-reactivity may occur if the patient ingested Oxaprozin, an anti-inflammatory drug [16].

Stimulants

Methamphetamine and prescription drugs such as Adderall (a dextroamphetamine and levoamphetamine salt mixture) or methylphenidate (Ritalin) are classified as stimulants by the National Survey on Drug Use and Health conducted by SAMHSA and will hence be covered here [6, 80]. Cocaine, an anesthetic, has stimulant-like pharmacological properties and is frequently used as a stimulant [81, 82].

The prevalence of methamphetamine for those over 12 years of age was approximately 0.2% or 595,000 users in the U.S. Routes of administration of methamphetamine are nasal insufflation, intravenous injection, oral ingestion and smoking [83]. The prevalence of prescription stimulant use amongst the general population in the U.S. by those over 12 years of age in 2013 was approximately 0.3% or 805,000 users [84]. Finally, the prevalence rate for cocaine use has been reported to be approximately 0.6% or 1.5 million users [6]. Cocaine is either snorted or injected intravenously in its hydrochloride salt form or smoked in a rock form commonly referred to as "crack cocaine" [85, 86].

Methamphetamine

Metabolites: The main metabolites found in the urine of methamphetamine users are amphetamine and 4-hydroxymethamphetamine, with some unchanged methamphetamine as well, depending on the pH level of the urine being analyzed [28, 87, 88]. More acidic urine will yield higher concentrations of unchanged methamphetamine as opposed to urine with more alkaline levels of pH [87]. Methamphetamine is a chiral compound with two different enantiomers occurring in nature, the levorotary enantiomer (*l*-meth) or the dextrorotary enantiomer (*d*-meth). While these compounds, *l*-meth and *d*-meth, may not differ much in terms of chemistry, they have very distinct pharmacological effects and are hence used for different purposes [88].

Testing window: The testing window for methamphetamine use is one (1) to four (4) days depending on duration of use, weight of the person being tested, metabolism, the route of administration, and body/fat composition [88]. Finally, the sensitivity, or "cut-off" concentration, of the test can affect the results as well [87].

Extraneous exposure: Some over-the-counter medications such as Vick's Vapor Inhaler, used as a decongestant, contain *l*-meth and can cause false positives on laboratory tests conducted on urine using standard LC-MS/MS methods to screen for methamphetamine [88]. Other drugs metabolize into l-meth, such as selegiline, also cause false positives. In order to distinguish between the two during a urine analysis, a chiral analysis must be conducted on the urine sample to determine the percent composition of each enantiomer present. This analysis has been determined to be the most accurate method of determining the proper source of the methamphetamine being detected [88]. Drug testing programs at Federal workplaces have determined that any percent composition of d-meth that is 20% or higher shows that either illicit methamphetamine, Desoxyn (d-methamphetamine HCL), or benzphetamine, which metabolizes into d-meth, is the source of the positive result. This can then be compared to the medical history and current medications of the person being tested to see if the result is due to either of the medications Desoxyn or benzphetamine, or if it is due to illicit methamphetamine use [88].

Special considerations: Research has shown a high-degree of poly-substance use among methamphetamine users. Methamphetamine users report using benzodiazepines to help with the methamphetamine "comedown" as well as prescription opiates such as Vicodin and OxyContin [89]. 3-4-methylenedioximethamphetamine (i.e., ecstasy) use is also common among methamphetamine users as are cannabis, GHB, alcohol and ketamine [90].

Pharmaceutical stimulants (Amphetamines, Methylphenidate)

Metabolites: The main metabolites of amphetamine-based pharmaceutical preparations (e.g., Adderall, Dexedrine, Vyvanse) include a mix of 4-hydroxyamphetamine and metabolized amphetamine that depends on the pH level of the urine being tested [87]. The pH level of the urine sample can have a great effect on the amount of unchanged amphetamines in the urine in a manner similar to methamphetamine (see above section on methamphetamine for more details). Methylphenidate (e.g., Ritalin, Concerta, Focalin) completely metabolizes in the body and does not appear as an unchanged drug in urine samples [91]. In fact, approximately 80% of the ingested dose of methylphenidate is metabolized into ritalinic acid.

Testing window: The testing window for amphetamine-related substances is one (1) to four (4) days. Weight,

dosing levels, body/fat composition, route of administration, individual differences in metabolism regarding amphetamines, and sensitivity of the urine analysis being performed all play a role in the four-day potential detection window [87, 88]. Methylphenidate has a similar detection window [91].

Extraneous exposure: As mentioned previously in the methamphetamine section, some over-the-counter and prescribed medications can create a false positive for either methamphetamine or amphetamines [28]. Immunoassay testing cannot distinguish methamphetamine and amphetamine from other medications such as pseudoephedrine. Thus, LC-MS testing should always be used to determine the exact substance in the urine, followed by a chiral analysis to determine which enantiomer is in the sample, d or l [28]. Medications that can trigger a false positive for methamphetamine, amphetamine, or methylphenidate include the following: Buproprion, Chlorpromazine, Dimethylamylamine, Labetalol, Metformin, Ofloxacin, Promethazine, Trazadone [92].

Special considerations: The drugs typically used by prescription stimulant users differ somewhat from those used by methamphetamine users. Binge drinking and cannabis use were the two most commonly reported substances used along with prescription stimulants in a study of college students [93].

Cocaine

Prevalence and route of administration: Cocaine use is reported by approximately 0.6%, or 1,785,000 Americans aged 12 or older with 0.1%, or 297,500 individuals reporting the use of crack cocaine [64]. The diagnosis of cocaine use disorder is less prevalent, encompassing 913,000 individuals or 0.3% of the population at 12 or older.

Metabolites and testing window: The major metabolite for cocaine is benzoylecgonine [82]. A study investigating cocaine and metabolite elimination patterns reported that cocaine half-life was longer than previously reported when sampling from a street using population, increasing from 1.25 h to 3.8 hrs. Additionally, benzoylecgonine's half-life remained unchanged with an average elimination of 7.5 hrs [94]. Conducting blood tests in order to screen for cocaine is not preferred as the screening window is only one to eight hours. The urine testing window will vary depending on the weight, fat/body composition of the individual, the urine pH of that individual, the sensitivity of the test being performed on the urine, the route of administration of the cocaine, and individual differences in metabolism [87, 88]. Average detection times for benzoylecgonine are approximately 49 hours [95].

Special considerations: A substance commonly used in conjunction with cocaine is alcohol [96]. Approximately 88% of people diagnosed with cocaine use disorder admitted to combining their cocaine use with alcohol. Whenever the two substances are mixed, cocaethylene is formed in the body, which is thought to contribute to the increased "high" and increased heart rate than when cocaine is used alone. While less potent than cocaine, cocaethylene produces effects so similar to cocaine that research participants could not discriminate [97-100]. However, cocaethylene can be found in the urine of only those who combine alcohol and cocaine together and has a testing window in-line with cocaine: one to four days [96, 101].

Cocaine use amongst patients undergoing methadone maintenance for heroin use disorder is also a commonly observed problem [86]. One study [86] examined the toxicology reports of eleven methadone maintenance programs and their 2,414 clients in the Baltimore, Maryland, area finding that between 5.9% to 33.0% of clients tested positive for cocaine in the 30 days leading up to the study . Of all 3,655 incoming methadone maintenance clients, 47.9% reported having "problems" with cocaine.

Opiates

Prevalence and route of administration

Opiates are used medically as analgesics or antitussives. The use of opiates may result in euphoria, respiratory depression, analgesia and physical tolerance [102]. The opiate class of drugs includes hydromorphone, hydrocodone, morphine, oxymorphone, oxycodone, codeine, and heroin. Although heroin is an illicit drug and is not prescribed for medical use, it is closely metabolically related to several opiates producing similar effects [60, 103]. In 2002, analgesic opioids accounted for 9.85% of all drug abuse and 0.0004% of patients prescribed an opioid for medical use developed a substance use disorder [104]. In 2013, the overall rate of narcotic use other than heroin for nonmedical purposes in the past year was 7.1%. In 2013, for those ages 18 - 25, 3.3% were current users of pain relievers for nonmedical purposes [84]. In 2013, approximately 0.2% (681,000 individuals) of respondents above the age of 12 were heroin users. Opiates can be used orally, through inhalation, intranasal or by injection (subcutaneously, intramuscularly or intravenously).

Special considerations

The detection of opiates varies greatly depending on the specific substance used. This is especially true of immunoassay methods. Since 1995, the Department of Health and Human services established the opiate concentration cutoff for immunoassays as 300 ng/mL [60]. However, due to the relatively high rate of false positive and false negative results, it should be assumed that immunoassays alone are not sufficient for accurate detection of opiates and should be followed by more advanced methods of testing. LC-MS has been shown to be a more accurate method of analysis than Immunoassay testing for opiates. Specifically, LC-MS can be used to detect the presence of opiates for up to 48 hours after administration, which is similar to the detection times of heroin administration [60]. In addition, liquid chromatography tandem mass spectrometry (LC-MS-MS) has been used for detection of opiates in urine and blood samples [102]. However, due to short half-lives (between 2.5 and 5 hours), opiate detection through blood samples is relatively limited compared to other methods.

Morphine

Route of administration: Morphine is organically present in *Pupuver somniferurn*, a poppy plant. Although morphine is almost totally absorbed from the gastro-intestinal tract, a thorough first pass metabolism of morphine leads to a low and varying bioavailability of approximately 19-47% [105]. The potency of some other opiates can be thought of in

terms of morphine. For example, oxycodone is thought to be equivalent to morphine but with a quicker bioavailability [60] or 2-4 more times effective [106], hydromorphone appears to be 8.5 times the strength of morphine, and oxymorphone is 10 times greater than morphine [60]. Approximately 90% of ingested morphine is converted into metabolites. Some of these metabolites are analgesics themselves including codeine and morphine-6-glucuronide will appear [105].

Special considerations: In order to determine the use of morphine, as opposed to other opiates that metabolize into morphine, there must be over 200 ng/mL and the proportion of legal drug to morphine should be less than 0.5. High-performance liquid chromatography has been shown to be capable of determining and meeting these two requirements [107]. When using LC-MS, the cut off concentration for morphine is 300 ng/mL according to the Department of Health and Human Services Guidelines [60]. A specific assay developed for the detection of morphine and its metabolites showed that after peroral morphine treatment, M6G and M3G were heavily concentrated and thus the area under the plasma time-curve was much greater than that of morphine itself. This finding led to the conclusion that these two metabolites may have a vital mediating role in the clinical and side-effects of morphine treatment [105].

Hydromorphone

Route of administration*:* Hydromorphone is a semi-synthetic analgesic opioid. It is typically prescribed for pain management and can be administered through immediate and slow release oral methods, intravenously, intrathecally, subcutaneously, and epidurally [108]. When taken orally, the onset of action generally occurs after 30 minutes with duration of approximately 4 hours after administration. However, modified-release preparations can have substantially longer durations of effect - from 12 to 24 hours. Despite being structurally similar to morphine the onset of hydromorphone is faster than that of morphine because it is more fat soluble. Hydromorphone is no more of a risk of abuse than any other opioid [104].

Metabolites: Hydromorphone acts on the μ opioid receptors and on the delta receptors, although to a lesser extent, to help alleviate pain and reduce side effects. Unlike morphine, hydromorphone does not have a 6-glucuronide metabolite, but is actually metabolized into hydromorphone-3-glucuronide and dihydroisomorphine glucuronide. The 3-glucuronide in hydromorphone is 2.5 times stronger than that in morphine as a neuroexcitant. Hydromorphone is not metabolized into an analgesically active 6-glucronide. Chronic usage of hydromorphone leads to blood levels of hydromorphone-3-glucuronide 30 times that of the parent drug, and renal failure can significantly increase this [104].

Oxycodone

Route of administration: Oxycodone is an opiate created from thebaine. One of its precursors is *Papaver bracteatum* which is highly toxic and not analgesic. Oxycodone can lead to a decrease in heart rate, increase serum prolactin levels and a decrease in S-cortisol. Oxycodone can be administered via oral routes, intramuscularly, intranasally, rectally, epidurally, and subcutaneously [109]. The drug effects peak at approximately 1 hour after administration and duration is approximately 4.5-5 hours.

Metabolites: Compared to morphine, the bioavailability of oxycodone is 40% greater. Its liposolubility is similar to that of morphine. Oxycodone is also found to be 2-4 times more effective than morphine. Oxycodone has two main metabolic pathways; through N-demethylation to noroxycodone and O-demethylation to oxymorphone. The compound concentrations vary depending on mode of administration with noroxycodone concentrations being much greater in urine and plasma when oxycodone is administered orally; this may possibly be due to a vital role of N-demethylation in the initial metabolization of oxycodone [106].

Testing window: The half-life of oxycodone varies based upon administration and it is excreted in urine as a free unconjugated form. The half-life is approximately 2 to 3 hours when administered intravenously, 3 hours in an immediate release form, and 8 hours in a controlled release form [109]. The maximum concentrations of oxycodone in plasma are reached are at 25 minutes intravenously, 1.3 hours in an immediate-release form, and 2.6 hours in a controlled-release form [106].

Oxymorphone

Route of administration and metabolites: Oxymorphone is an opiate with greater analgesic properties than morphine and is estimated to be 10 times stronger than morphine [60, 110]. Oxymorphone can be administered orally in an immediate-release and sustained-release form, intravenously, subcutaneously, and rectally. The oral bioavailability of oxymorphone is low at 10% and its half-life varies between 7.2 and 9.4 hours. Oxymorphone usually takes 30 minutes to reach peak concentration. Plasma concentrations show a peak after 4 hours of administration and after 12 hours decrease by only 30%. Through an intravenous or subcutaneous routes, peak action is reached within 5 to 15 minutes, and has a duration between 3 to 6 hours [110]

Testing window: Oxymorphone is structurally similar to hydromorphone and is more lipid soluble than morphine due to a ketone-group substitution. In urine, less than 2% of the parent drug is excreted. In healthy patients, 33 to 38% of oxymorphone 3-glucuronide is excreted in urine. After the first 24 hours of a 10 mg oral administration, 82% of a total 49% in a 5 day period of oxymorphone 3-glucuronide was excreted via urine [110].

Heroin

Route of administration: Heroin is produced from opium poppies and is most stable at 0-4 °C and at a pH between 3.5 and 5.2. Heroin is a semi-synthetic morphine derivative which is lipophilic. In the past, heroin was not typically blended or abused with other drugs, however among young people and in certain countries, such as Japan, methamphetamine has been commonly seen blended with heroin [103].

Metabolites: The bioavailability and metabolization of heroin is affected by the method of administration. In heroin inhalation, the bioavailability is limited because the vaporization procedure leads to a degradation and a portion of the heroin is lost. Compared to intravenous use, inhalation

led to elevated levels of morphine-6-glucuronide, and the level of glucuronides appears similar to that following the oral administration of morphine possibly because when heroin is inhaled a portion is absorbed through the digestive tract [101].

Testing window: Due to the way in which heroin is metabolized, detection in urine samples is rare unless the sample is given immediately following administration [103]. Heroin has an extremely short half-life which is approximated to be between only 2 and 5 minutes [111]. One of its main active metabolites, 6-acetylmorphine (6-MAM), has a half-life of 5 minutes [103]. Despite the short half-life of heroin, it appears to have an extended pharmacodynamic action of multiple hours [111]. Heroin has 3 known main metabolites. These are an inactive metabolite, normorphine, an active metabolite, morphine, and an active metabolite which is not a pharmaceutical opioid, 6-Monoacetylmorphine [112]. Due to its brief half-life, heroin is quickly metabolized by liver esterases or serum or suddenly hydrolyzed into MAM which is then hydrolyzed into morphine [103, 111].

Special considerations: As morphine is a metabolite of heroin, the use of heroin is often confirmed with immunoassays by morphine. However, this leads to problems as morphine is a metabolite of several other opioids. For example, codeine, often used in cold medicine, metabolizes into morphine, thus the presence of morphine alone is not a sufficient indicator for heroin use. Therefore, the presence of MAM is necessary to confirm the use of heroin. Unfortunately, MAM has a brief window of detection in urine of 2 - 8 hours [103]. In addition, urine analysis can lead to different opioids being mistaken for one another because of overlapping metabolites. However, the presence of 6-MAM is the only definitive proof of heroin use [113].

Common Hallucinogens (LSD, Mescaline, Psilocybin, PCP and DMT)

If they are tested for, hallucinogens are typically detected using blood and urine analysis, although concentrations of the drugs and/or their metabolites in samples are usually very low making confirmation difficult.

Lysergic acid diethylamide (LSD)

Prevalence and route of administration: A survey conducted by the National Survey on Drug Use and Health revealed that in 2013, about 24.8 million Americans age twelve and older used LSD (d-lysergic acid diethylamide) at least once in their lifetime. Furthermore, 1.1 million of Americans ages twelve and older used LSD at least once in the year before the survey was conducted [114]. A 2006 study revealed that LSD is more likely to be used by females than males. LSD is also more popular among people with low-income backgrounds. LSD is categorized as a club drug, or a drug commonly used in raves, parties, concerts, and similar events. Therefore, the primary users of LSD are attendees of these events, mainly adolescents and young adults [115]. LSD is primarily administrated orally in the form of a tablet or capsule. It can also be obtained as a liquid. In that case, the user can apply the liquid LSD to an absorbent paper and ingest the drug that way [114].

Metabolites and testing windows: The major metabolite of LSD (d- lysergic acid diethylamide) is 2-oxo-3-hydroxy-LSD (O-H-LSD). The half-life of LSD is three to four hours. Currently, there is no well-established detection window for blood testing. The detection window for LSD in urine is 12-22 hours, however the window is larger when O-H-LSD is the target analyte. Some drug testing labs propose the use of a 24-72 hour detection window.

Extraneous exposure: There have been some instances where urine tests for LSD have produced false positive results. For example, the drug ambroxol in urine samples has been shown to produce false positives for LSD in CEDIA DAU assays, a homogenous enzyme immunoassay. When patients who tested positive were retested with high performance liquid chromatography, they produced negative results for LSD [116]. In a separate study, it was found that certain psychiatric or medical drugs interfered with urine samples that were tested by EMIT assays, showing positive results for LSD when multiple other methods showed negative results. Some of these psychiatric drugs include Doxepin, Fluoxetine, and Sertraline [117].

Special considerations: The vast majority of LSD users use multiple drugs from numerous drug classes, including other club drugs [115]. For example, LSD has been known to be taken with MDMA, commonly known as ecstasy, and ketamine [118]. The combination of LSD and MDMA, or "candy flipping," is extremely popular. However, scientific literature on combinations of drugs and their effects is limited. As a result, some researchers use informal and anecdotal websites from the Internet to learn more about drug culture [119].

Psilocybin

Prevalence and route of administration: Psilocybin prevalence has risen dramatically in the last two decades, particularly among adults ages 30-34. While only an estimated 5% of US residents (10.2 million) reported having tried psilocybin mushrooms in the 1997 National Survey of Drug Use and Health, data from the 2010 survey revealed that approximately 21 million US residents had used Psilocybin in their lifetime. While, outside of laboratory settings, psilocybin can be prepared synthetically, it is not typically administered in this form. The psilocybin present in certain species of mushrooms can be ingested in several ways: by consuming fresh or dried fruit bodies, by preparing a herbal tea, or by combining with other foods to mask the bitter taste [120]. In rare cases, people have injected mushroom extracts intravenously [121].

Metabolites and testing windows: Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is the primary psychoactive ingredient in psychedelic mushrooms. Its major metabolite is psilocin, which forms in humans one hour after ingestion. Psilocybin has a 1.8-4.5 hour half-life. Like other hallucinogenic drugs, psilocybin is uncommonly tested for using blood analysis and there has yet to be an established detection window for this type of testing. The detection window for urinalysis is less than a day for single use and up to three days for chronic users. Because psilocybin and its metabolites

are structurally derived from tryptamine, a monoamine, they are quickly metabolized by monoamine oxidase making them difficult to detect after use. An additional difficulty with urinalysis lays in the fact that psilocin, which is present in urine after use, rapidly degrades with exposure to light.

Special considerations: In mainstream drug culture, psilocybin is most commonly combined with MDMA. This usage, known as "hippy flipping," can be most precisely understood through the chemical relationship of both drugs: the primary neurotransmitters effected by psilocybin and MDMA is serotonin. MDMA releases large quantities, or "dumps," serotonin throughout the brain while psilocybin binds to serotonin receptors, inducing intense, disorientating euphoria unique to the drug [122].

Because most hallucinogenic drugs operate upon serotonergic systems, a small number of studies have identified the interaction between psychedelics and antidepressants in recreational settings. A study conducted by Bonson and Murphy [123] suggests that chronic use of tricyclic antidepressants and lithium may increase the subjective effects of psychedelics whereas chronic use of SSRIs and MAOIs may reduce the subjective effects of [124].

Dissociative Drugs (PCP, DXM and Ketamine)

Phencyclidine (PCP)

Prevalence and route of administration: The National Survey on Drug Use and Health indicates that in 2013, the lifetime prevalence of PCP use in the US was 2.5% for people above the age of 12, with 0.20% falling in the age category of 12-17 years [6]. PCP can come in the forms of a tablet or capsule, liquid, crystal, and powder. It can be snorted, injected, smoked or ingested. Inhalation is the most popular method of administration, as users can feel high in only about two to five minutes [124].

Metabolites and testing windows: The major metabolites of PCP found in urine are hydroxylate and glucuronide. PCP has an average half-life of 21 hours with a wide range of 7-46 hours. As a nonpolar substance, PCP is stored in the body's fatty lipid tissues for several weeks following use. Thus, individuals with greater body mass generally have a larger detection window. For urinalysis, the detection window is three to seven days for single use, or up to 30 days for regular use. For blood testing, the detection window is one to three days, and up to 90 days for hair testing [125].

Special considerations: PCP can be used in conjunction with cannabis when users dip a marijuana cigarette into liquid PCP or add in powdered PCP [126].

Dextromethorphan (DXM)

Prevalence and route of administration: As a popular ingredient in many over the counter cough and cold medicines, Dextromethorphan is relatively cheap, easy to access, and legal to obtain. Due to these factors, there is concern over the recreational use of DXM, especially by adolescents. However, data gathered within the last decade seem to suggest that the non-medical use of DXM is on the decline. The Monitoring the Future (MTF) Survey of the University of Michigan reported that, in 2014, 2% of eighth graders, 3.7% of tenth graders, and 4.1% of twelfth graders used DXM to get high [127]. DXM can be administered orally in the form of a capsule, tablet, or syrup, the latter being more popular. DXM can also be obtained and consumed as a pure powder [128].

Metabolites and testing windows: The major metabolites of DXM are dextrorphan, 3-methoxymorphinan, and 3-hydroxymorphinan. DXM has a biological half-life of two to four hours. It is primarily excreted as unchanged DXM and dextrorphan. 24-hours following use, 2.5% of consumed DXM is excreted in urine unchanged while 30% is excreted in urine as dextrorphan [129]. DXM is not commonly tested for during drug tests and there has not been established a detection window for any mode of tests.

Special considerations: About 5-10% of individuals of European ethnicity lack an enzyme that efficiently breaks down DXM, putting them at higher risk of adverse effects [130]. Additionally, DXM is sometimes taken in combination with heroin [131].

Ketamine

Prevalence and route of administration: About 1% (2,720,000 individuals) of Americans reported ever having used ketamine in 2013, with approximately 0.1% (274,000 individuals) reporting use in the previous year [6]. Ketamine can be ingested intranasally, smoked with marijuana or tobacco cigarettes, injected intravenously, or mixed in drinks [132].

Metabolites and testing windows: The major metabolites of ketamine are norketamine and dehydronorketamine. Following intravenous use, the biological half-life of ketamine is about 2.3 hours [133]. The detection window for the presence of ketamine and norketamine in urine is five to six days and up to 10 days for dehydronorketamine [134].

Special considerations: Ketamine can be combined with marijuana & tobacco and possibly ingested unknowingly; it can also be mixed into drinks to "facilitate sexual assault" [132]. Users often combine ketamine with methylenedioxymethamphetamine (MDMA, or Ecstasy), amphetamine, methamphetamine, cocaine, and marijuana [135]. Ketamine is not tested for in standard drug tests, however due to its increasing use as a date-rape drug, testing for it is becoming of more interest and a more common practice.

Emerging Drugs (MDMA, GHB, and Synthetic Cathinones)

3,4-Methylenedioxymethamphetamine (MDMA)

Prevalence and route of administration: About 6.8% (17.8 million) of Americans reported having used MDMA in their lifetime in 2013 [6]. MDMA is most commonly taken as a tablet, but is occasionally crushed and snorted or added to marijuana; it is rarely injected [132].

Metabolites and testing windows: The major metabolites of MDMA (3,4-Methylenedioxymethamphetamine) are 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxyamphetamine (HMA), and free and glucuronidated/sulfated 4-hydroxy-3-methoxymethamphetamine (HMMA) [136]. MDMA has a half-life of six to nine hours. The

detection window of MDMA in urine is one to seven days. Because MDMA is an amphetamine derivative, many drug tests will result in false positives for amphetamines in addition to a true positive result for MDMA.

Special considerations: As a popular "club drug", MDMA is commonly combined with alcohol, cocaine, hallucinogenic drugs, as well as THC. Some users of MDMA participate in a common trend of "candy flipping" where MDMA and LSD are taken together. Often ecstasy tablets consist of MDMA mixed with other harmful drug combinations such as methamphetamine, ketamine, cocaine, and caffeine [132].

Gamma-Hydroxybutyrate (GHB)

Prevalence and route of administration: About 0.6% (1.5 million) of Americans reported having used GHB in their lifetime in 2013 [6]. GHB is often found in liquid form, but it is also possible to find GHB in a tablet or powder form and it can be taken orally or intravenously [132, 137]. Within the club scene, 21.5% of the sample had ever used GHB in which 5% of that population used GHB within the past four months. Men were 6.13 times more likely than women to have reported recent use of GHB. Frequency of drug use in the last four months by GHB users was reported to b 1.5 medium days of use. Gay and bisexual men (34.0%) were more likely than lesbian and bisexual woman (13.0%) and heterosexual women (16.0%) to have ever used GHB [138].

Metabolites and testing windows: The major metabolite of GHB is succinic acid. GHB has an average biological half-life of 27 minutes, with a range of 20-53 minutes. Due to the body's elimination of the drug, GHB is undetectable in blood after 6-8 hours [139]. In urine, peak concentrations of GHB are found four hours after ingestion and then is rapidly eliminated, making it undetectable 10-12 hours after use. Endogenous GHB has been found in concentrations of up to 7 mg/L in the urine of non-users, therefore any amount present in higher concentrations may suggest the consumption of exogenous GHB.

Special considerations: GHB, along with its precursor drugs, are frequently used in combination with MDMA, alcohol, marijuana, cocaine, methamphetamine [57]. A majority of Australian GHB users reported typically using GHB with ecstasy [140].

As a metabolite of the major neurotransmitter gamma-aminobutyric acid (GABA), GHB is naturally present in the body and can this can lead to false positives when testing for it. However, endogenous GHB is usually found in small concentrations in blood, usually below 1mg/L in living people [139], therefore any amount present in higher concentrations may suggest the presence of exogenous GHB.

Synthetic cathinones ("Bath Salts")

Prevalence and route of administration

Cathinone, also referred to as "Cat", is the parent drug from which synthetic analogues are developed and sold as legal high throughout the world [141]. A literature review concerning the prevalence and route-of-administration of synthetic cathinones reviewed over 80 articles published between 2004 and 2012 from western countries, determining that the prevalence of synthetic cathinones at the time was about 4% amongst the general population, 1-20% for college students, and 4-60% for "groups of high drug use" [142]. Hence, synthetic cathinones can be swallowed, insufflated nasally, injected either directly into the muscle or intravenously [141].

Metabolites

Analogues are developed in a lab using chemical reactions to alter the original cathinone compound, usually through aromatic substitution (replacing a hydrogen atom attached to the benzene ring of cathinone with a methyl group) or by altering the primary amine by replacing a hydrogen bonged to the nitrogen with a methyl group [142]. The most common synthetic cathinones are methedrone, methylone, mephedrone, and methylenedioxypyrovalerone (MDPV), but others exist as well [143]. Due to the similar chemical structure to amphetamines, cathinones and synthetic cathinones produce very similar effects to amphetamines, while also interacting with serotonergic systems well. Some identified major metabolites for butylone, ethylone, and methylone are 4′-hydroxy-3′-methoxymethcathinone, 3′-hydroxy-4′-methoxymethcathinone, and butylone, ethylone, or methylone, unchanged in urine [141, 143].

Testing windows

Despite the prevalence of synthetic cathinone use, detection through typical drug screening can be difficult for these compounds as very few reliable methods of screening have been made available [144]. Further, the exact amount and identities of the compounds ingested by anyone who uses "bath salts" is typically unknown and can contain new chemicals that have never been tested before, further complicating the process of drug screening. The list of synthetic cathinones continues to grow as more synthetic chemicals are created in order to stay ahead of the changing laws. In one human subject who ingested a dose of methylone at 5 mg/kg, the unchanged methylone was detectable in urine for approximately 36 hours while the metabolites where detectable up to 48 hours.

Special considerations

Users of synthetic cathinones tend to be poly-drug users, as over 80% of respondents, when asked about the mephedrone use, reported either mixing other drugs of abuse with mephedrone or using other drugs at different times [141]. The drugs reported included cannabis, cocaine, MDMA, and alcohol. Users of MDPV who ended up in the emergency room also tested positive for ethanol and benzodiazepines [141]. There is no particular drug combination that is preferred over others for synthetic cathinone users, and not all users abuse other drugs along with synthetic cathinones, but there is evidence that poly-substance abuse is of concern with this classification of drug.

While mephedrone and MDPV are now illegal due to legislature that was passed in 2012 to permanently ban the substances, producers of the drugs are expected to continue to alter the chemicals in order to create new "designer drugs" that will not be legal to sell as long as producers clearly label the package with "not for human consumption" in order to comply with The Federal Analogue Act of 1986, which prohibits the

manufacture and possession of any analogue of a scheduled I or II substance if it is intended for human use [141, 143, 145]. The Federal Analogue Act listed the following substances: butylone, dimethylcathinone, ethcathinone, ethylone, 3-fluromethcathinone, 4-fluromethcathinone, mephedrone, methcathinone, methedrone, MDPV, methylone, and pyrovalerone [143].

Recommendations for Best Practice

Recommendations for drug testing in treatment

The comprehensive review of testing methods, drugs of abuse, and current standards available in the field is meant as a preface to the establishment of a standard testing procedure within SUD treatment settings. The goal of utilizing any method of drug testing is to assess patient progress and treatment adherence and to potentially increase treatment efficacy rates by providing valid assessments of success and reliable indications of further treatment need. As mentioned earlier, the current lack of standard protocols for drug testing is likely negatively impacting the utility of drug testing within MHSUD settings. Given the research review we have conducted, we recommend the following standard procedure for MHSUD settings:

1. At intake, clients should be asked to provide urine for a comprehensive analysis of their recent substance use. Additionally, clients should be asked to provide, as is customary, a complete history of their substance use. The results of the initial urine screen should be compared to the self-reported substance use history to assess for consistency and reliability of the self-reported substance use. We recommend that any inconsistencies, such as additional substances identified through urinalysis or unexpected exclusions in the urinalysis, should be directly discussed with the patient. Such discussions should be presented as reviews of standard medical tests and not as opportunities to confront patients about misrepresentations. This is especially true when illicit substance use is involved as illicit drug sources have been known to provide adulterated substances, which clients may be unaware of (CITATION).
2. After the initial screening, testing for each client should consist of urinalysis and/or saliva testing using a consistent schedule that takes into consideration the detection window for the testing methods being used and for the substances being tested for. The most typical window, which should provide adequate testing validity for most commonly used substances, is three-days. This may require some individualization of testing schedules for specific clients. The change in testing methods should make specimen adulteration difficult over and above the standard validity tests as saliva tests are more easily monitored and more difficult to alter. The use of consistent testing schedules, rather than randomized testing, should reduce resistance to testing and increase the likelihood of testing being considered a standard treatment process. Additionally, ongoing testing should provide a more consistent and valid assessment of ongoing drug-use, avoiding the possibility of identifying client drug use a considerable time-period after its initiation. The post-intake screenings should assess the SAMHSA-5 as well as any additional substances that were identified in the comprehensive initial screen, as being recently used through client self-report, and any psycho-therapeutic medication being administered.
3. We recommend that testing for alcohol take the form of breathalyzer testing with, or without, urinalysis. The inconsistent detection-window for alcohol as well as the relatively high risk for environmental contamination suggests that more time-sensitive and alcohol-specific methods should be used particularly for clients who present for alcohol treatment. While having a client report regularly for breathalyzer testing at a facility is not feasible, especially in outpatient setting, the use of mobile breathalyzers that offer secure portals for treatment staff reporting are recommended in such instances. Such testing allows for a more consistent and valid assessment of alcohol consumption among individuals in treatment and has been shown to produce more accurate reporting of alcohol consumption [53].
4. At random intervals, but no less often than once per month, a comprehensive screening should be undertaken in order to identify any possible changes in substance use patterns. This practice should allow for the detection of the initiation of use of replacement substance, such as synthetic cannabinoids or stimulants, post treatment intake while controlling the cost of ongoing use of comprehensive screens.
5. Clients should be provided information about the results of their drug testing in all cases – positive feedback should be provided when testing results indicate no unexpected substance use while providing the appropriate treatment intervention when results reveal problematic substance use. Some research indicates that the availability, and provision, of testing results to more than the client alone can result in greater adherence although this obviously requires the appropriate medical health information releases to be in place and all transmission of such information should adhere to HIPPA regulations.

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