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Buprenorphine Medical Management Part 2: Monitoring the Patient

Action Period Assignment from 8/26

- *Think of 3 social history questions NOT directly related to substance use which may help you diagnose an SUD in a patient.*

- *Based on what you learned on 8/26, what office practices can you implement that might help you in diagnosing a substance use disorder in a patient?*

Presentation Outline

- Part 1: Drug testing basics
- Part 2: Presumptive and definitive testing
- Part 3: Monitoring buprenorphine compliance
- Part 4: Specimen validity
- Part 5: Other testing matrices
- Part 6: Case discussions

Reference:

Appropriate Use of Drug Testing in Clinical Addiction Medicine

Jarvis M, Williams J, Hurford M, Lindsay D, Lincoln P, Giles L, Luongo P, Safarian T. Appropriate Use of Drug Testing in Clinical Addiction Medicine. J Addict Med. 2017 May/Jun;11(3):163-173. doi: 10.1097/ADM.0000000000000323. PMID: 28557958.

Available online:

https://www.asam.org/docs/default-source/quality-science/appropriate_use_of_drug_testing_in_clinical-1-(7).pdf?sfvrsn=2

Part 1:

Drug Testing Basics

Drug Testing Basics

- Drug testing provides another source of information to **complement self-report, collateral report, and provider assessment.**
  - Drug testing should not be relied upon as the sole measure of a patient's substance use.

- Drug testing provides an additional, alternative means of assessing a patient's recent substance use and is important to treatment planning and ongoing treatment adjustment.

- Drug testing should NOT be used as a means to "catch" a patient in the midst of unauthorized substance use.

Drug Testing Basics

- A positive drug test is **not** sufficient evidence for a diagnosis of an SUD.
- A drug test does not measure impairment and in most cases a drug test does not measure patterns of use over time.
- A negative result does not mean that a patient has not used substance: **It means that the patient has not used the substance(s) targeted by the test within the window of detection or used an amount less than the test is capable of detecting.**

Drug Testing Basics

- Every effort should be made to persuade patients that drug testing is a therapeutic, rather than punitive, component of treatment.
- Test results that do not align with a patient's self-report should generate therapeutic discussion with the patient
- Providers should use negative test results as a source of encouragement: **Drug testing may serve as a source of motivation and reinforcement for abstinence**.

Terminology

- **Unexpected test results**: an unexpected test result could be (a) negative for prescribed medication, (b) positive for other addictive substance, or (c) both.

- **Expected test results**: an expected test result is positive for prescribed medication and negative for other addictive substances.

- In the context of addiction treatment that includes medication, the terms **positive and negative** have been replaced with **"unexpected" and "expected."**

Refusal to Drug Test

- If a patient refuses a drug test, the refusal itself should be an area of focus in the patient's treatment plan.
- "My way or the highway" approach should be avoided; however, the importance of the test and their continued compliance with treatment should be emphasized.
- Appropriate changes to the treatment plan may be a consequence of drug test refusal, including discontinuing buprenorphine.

Testing Frequency

- **There is very little guidance about clinically appropriate test schedules, which has led to both an over and under-utilization of drug testing.**

- The provider's therapeutic questions should dictate the frequency of drug testing.

- Providers should be aware that there is currently insufficient evidence that more frequent testing leads to decreased substance use.

Testing Frequency

"The Expert Panel recommends that a patient in early recovery be tested at least weekly. As the patient becomes more stable in recovery, the frequency of drug testing should be decreased, but performed at least on a monthly basis. Individual consideration may be given for less frequent testing if a patient is in stable recovery."

Jarvis M, Williams J, Hurford M, Lindsay D, Lincoln P, Giles L, Luongo P, Safarian T. Appropriate Use of Drug Testing in Clinical Addiction Medicine. J Addict Med. 2017 May/Jun;11(3):163-173. doi: 10.1097/ADM.0000000000000323. PMID: 28557958.

Other clinical considerations

- Clinical consensus favors unannounced drug testing over scheduled drug testing and random testing schedules to fixed testing schedules.
  - Unannounced or random drug testing may be difficulty to implement in a primary care setting.

- Observed testing is not recommended by this presenter, for a patients engaged in out-patient SUD treatment in a primary care setting.

Part 2:

Presumptive and Definitive Testing

Presumptive Testing

- Uses immunoassay technology.
- **Positive results are presumptive and NOT definitive**
- Presumptive tests generally have lower sensitivity and/or specificity compared to definitive tests.
- Faster turnaround time.
- Often called "qualitative tests" because they are designed to measure the presence or absence of the target drug/analyte, rather than the amount.

Presumptive Testing

- Positive presumptive test results should be referred to as "presumptive positive" results until confirmed by a definitive test.
- If a patient disputes the results of a presumptive test, the test should be confirmed using a **definitive method**.
- If a patient confirms that he or she used a substance detected by a presumptive test, it is not necessary to perform a definitive test to confirm the result.

Definitive Testing

- Uses a combination of various chromatography and mass spectrometry techniques, often referred to as GC/MS.

- **The results of a definitive test can be taken as conclusive.**

- Definitive testing should be used whenever:
  - A patient disputes the findings of a presumptive test.
  - When a provider wants to detect a specific substance not adequately identified by presumptive methods (eg, heroin rather than opiates).
  - When the results will inform a decision with major clinical or non-clinical implications for the patient.

Amphetamines

- Standard amphetamine immunoassays target amphetamine, which is also a direct metabolite of methamphetamine.

- Amphetamine immunoassays are also subject to many false-positives compared to other drug class assays.
  - Vicks Inhalers contain L-methamphetamine.
  - Therapeutic use of **bupropion** (Wellbutrin) appears to be the most frequent cause of false positive urine drug screens for amphetamine.

Benzodiazepines

- Immunoassays are generally not sensitive to therapeutic doses of benzodiazepines
- Most general benzodiazepine assays have very low sensitivity to **clonazepam and lorazepam.**
- If a patient's benzodiazepine immunoassay is negative, but the patient states that he or she is taking their medication as prescribed, providers can request **a definitive test** if they wish to confirm use.

Opioids

- A standard opiate immunoassay will detect the use of morphine, codeine (which is metabolized to morphine).
  - They show moderate cross-reactivity with the morphine-derived semi-synthetics **hydrocodone and hydromorphone,** and poor cross-reactivity with thebaine derived semi-synthetics **oxycodone and oxymorphone**

- Heroin (diacetyl-morphine) is metabolized to 6-mono-acetyl morphine (6-MAM) and then to morphine.
  - Heroin or 6-MAM must be detected to confirm the use of heroin.

- Consumption of poppy seeds can result in a positive opiate immunoassay test result and patients should be instructed to avoid the consumption of poppy seeds.

Opioids

- Oxycodone and oxymorphone (a metabolite of oxycodone) are detected in a few but not most standard opiate immunoassays
  - One author listed the cross-reactivity of standard opiate immunoassays with oxycodone as ranging between 1% and 10% in 2012.

  Dasgupta A. Resolving Erroneous Reports in Toxicology and Therapeutic Drug Monitoring: A Comprehensive Guide. Hoboken, NJ: John Wiley & Sons; 2012.

- Meperidine, methadone, buprenorphine, and fentanyl will not be detected in a standard opiate immunoassay and require their own test.

Cocaine

- Urine testing targets the cocaine metabolite benzoylecgonine (BZE) as cocaine itself has a very short half-life.
- Compared with opiate, benzodiazepine, and amphetamine tests, presumptive tests for cocaine are more **sensitive and specific.**
- **The immunoassay is very specific for cocaine metabolites and thus this is considered a definitive test**

Part 3:

Monitoring Buprenorphine Compliance

Buprenorphine Monitoring

- Urine testing for buprenorphine is a common way to monitor adherence.
- Within the past few years, there has been an increasingly recognized practice of patients adding buprenorphine to their urine to simulate prescription adherence ("spiking").
- Practitioners may rely upon the concentration of norbuprenorphine (metabolite) to buprenorphine (N:B) to discern possible evidence of tampering.

Warrington JS, Warrington GS, Francis-Fath S, Brooklyn J. Urinary Buprenorphine, Norbuprenorphine and Naloxone Concentrations and Ratios: Review and Potential Clinical Implications. J Addict Med. 2020 Jun 9. doi: 10.1097/ADM.0000000000000676. Epub ahead of print. PMID: 32530884.

Buprenorphine Monitoring

- "Spiking" a urine specimen: dissolving a small portion of the buprenorphine tablet or film directly into the urine to create a positive result that simulates adherence to buprenorphine.

- Routine buprenorphine immunoassay tests report results as positive or negative and **cannot** distinguish between the patient who is taking buprenorphine as prescribed from the patient who has spiked the urine

Suzuki J, Zinser J, Issa M, Rodriguez C. Quantitative testing of buprenorphine and norbuprenorphine to identify urine sample spiking during office-based opioid treatment. Subst Abus. 2017 Oct-Dec;38(4):504-507. doi: 10.1080/08897077.2017.1356796. Epub 2017 Jul 19. PMID: 28723256.

Buprenorphine Monitoring

- Buprenorphine is metabolized to norbuprenorphine, which persists much longer than buprenorphine in the body and accounts for much of the mechanism of action.
- Quantitative testing may help identify spiking by examining the levels of buprenorphine compared to norbuprenorphine.
- In compliant treatment, norbuprenorphine concentrations will be greater than buprenorphine, resulting in an N:B ratio of greater than 1.0
  - One study indicating a mean ratio of 2.9 in non-spiked samples.

Suzuki J, Zinser J, Issa M, Rodriguez C. Quantitative testing of buprenorphine and norbuprenorphine to identify urine sample spiking during office-based opioid treatment. Subst Abus. 2017 Oct-Dec;38(4):504-507. doi: 10.1080/08897077.2017.1356796. Epub 2017 Jul 19. PMID: 28723256.

Buprenorphine Monitoring

- Spiking of the urine will elevate buprenorphine levels significantly but not norbuprenorphine, because the dissolved tablet does not contain norbuprenorphine.

- In one study, all spiked urine samples contained norbuprenorphine, suggesting that patients were taking at least a portion of their prescribed buprenorphine *(Suzuki et al).*

Part 4:

Specimen Validity

Specimen Validity Testing

- Specimen validity testing indicates:
  - that a sample has been tampered with by detecting the presence of adulterants or
  - the absence of biological indicators of normal human urine.
- Definitive testing should always include specimen validity testing which measures **creatinine concentration, pH level, and specific gravity**.
- Not all adulterants can be detected in standard adulterant test, including **Visine eye drops** and newer adulterants such as **Urine Luck, UrinAid, Klear, and Whizzies.**

Creatinine

- Creatinine is the product of muscle metabolism and is produced at a fairly constant rate by the body.
- Creatinine will be very low if an individual has over-hydrated, and very high concentrations can result from the use of some adulterants.
- SAMHSA has set criteria for normal creatinine concentrations in urine, with **<20 mg/dL** indicating a **dilute sample**. This limit is meant to screen out probable instances of attempted tampering among the general workplace population.

Specific Gravity

- Specific gravity is a measure of the concentration of dissolved particles in a liquid by comparing its density to the density of water.
- The specific gravity of normal human urine is between 1.003 and 1.030.
- While a urine specific gravity of 1.000 is essentially water and suggest dilution, higher specific gravity values can indicate that an adulterant has been added to a sample.
  - For example, the amount of table salt needed to produce a false-positive, results in specific gravity over 1.035.
- Most sources recommend that specific gravity need only be checked if creatinine is <20 mg/dL.

Urine pH

- pH ranges between 4.5 and 8.0 in urine.
- pH of the sample may influence the enzymatic action and performance of immunoassay screens. Abnormal pH can indicate that a sample is dilute or adulterated.
- Bleach, acid, soap, detergent and vinegar all alter pH to outside the normal human range.
- Abnormal pH can also be the result of a kidney or urinary tract infection as well as diets extremely high in protein or low in carbohydrates.

Adulterants

- Testing for the presence of adulterants such as glutaraldehyde, pyridium chlorochromate and nitrites can be done on-site or in a laboratory.
- Not all adulterants can be detected in standard adulterant test, including Visine eye drops and newer adulterants such as Urine Luck, UrinAid, Klear, and Whizzies .

Unusual Specimen Characteristics

- Unexpected temperature
  - A recently provided sample should be within expected body temperature range, approximately **90 to 100 degrees** within 4 minutes of production.
  - Too cold: a substitute sample or cold liquid was added to the sample.
  - Too hot: a chemical heat pack like a hand warmer was used to try to mask the addition of a cold liquid.
- Unusual color
- Unusual smell
- Soapy appearance, cloudiness or particles floating in the liquid

Abnormal urine appearance can also be the result of a urinary tract infection, kidney stones, yeast infection, diet (eg, beets, asparagus) and the use of over-the-counter vitamins and medications (eg, ex-lax, Vitamin B)

Visual Inspection of Urine

- Dilute urine is lighter in color than normal urine, which ranges from light/pale yellow to dark/deep amber.
- Nitrites also tend to make the color of urine dark.
- Urine that has been diluted with liquids such as vinegar, ascorbic acid and rubbing alcohol can sometimes be detected by their distinct smell.
- Table salt (sodium chloride) and denture tablets may be visible as undissolved granules.
- Dish and hand soap will give the sample a soapy appearance.

Dilute Urine Samples

- A combination of low creatinine (below 20 mg/dL) and specific gravity is used to indicate that a sample is dilute.
- Most common cause of an invalid sample.
- ASAM expert panel members commented that dilution is usually the result of deliberate water loading.

Dilute Urine Sample

- For patients with a history of dilute urine samples, providers should:
  - Advise the patient to decrease water intake prior to sample collection
  - Collect samples first thing in the morning
  - Collect samples before work or on days off (if a patient's occupation involves the need to hydrate heavily)
  - Consider the use of an alternative matrix

Part 5:

Other Testing Matrices

Oral Fluid Testing

- Drugs are present in oral fluid primarily through:
  - passive diffusion from the bloodstream to salivary glands and
  - absorption and excretion by mucous membranes in the oral cavity during ingestion or inhalation.
- Because oral fluid testing is primarily blood-based, oral fluid drug concentrations generally correlate with plasma concentrations.
- Offers a shorter window of detection than urine (12–48 hours for most substances).
- Oral fluid has gained attention as a possible replacement for urine as the matrix of choice in drug testing.

Hair Testing

- Hair can be thought as a continuous collection device which absorbs compounds as blood passes through the hair follicle sweat gathers and is absorbed around the base of a growing hair shaft.
- Scalp hair is the most commonly tested sample, but pubic, armpit and facial hair can be also be used.
- Head hair provides a window of detection of approximately 3 months; body hair, which grows much more slowly, can be used to detect use up to 12 months.
- **The routine use of hair testing is not appropriate for most addiction treatment settings**

Part 6:

Case Discussions

Case 1

- You recently started a 42 year-old female on buprenorphine due a 3 year history of IV heroin use. She has been compliant and doing well.

- 2 months into her treatment, a urine drug screen is positive for amphetamine. She adamantly denies use, and you send the sample for definitive testing, which shows L-methamphetamine.

- What do you do?

Case 1 Discussion

- Methamphetamine, having a chiral center, exists as *d*- and *l*-enantiomers and is designated as a controlled substance without discrimination of its enantiomer.
- The *d*-enantiomer exerts potent physiological and psychostimulant effects and has high abuse liability.
- The *l*-enantiomer exerts almost none of these effects and is present in some OTC nasal decongestants.

Case 2

- An 18 year-old male is doing well on buprenorphine 8 mg bid, but suffers a broken leg after a fall and necessitates orthopedic surgery.
- Post-operatively, the patient is prescribed Vicodin (hydrocodone) which is dispensed to him by his mother, who is familiar with his history.
- During your follow-up visit, his UDS is positive for opiates which shows hydromorphone after GC/MS confirmation. He denies the use of any opioids other than buprenorphine and Vicodin.
- What do you do?

Case 2 Discussion

- Hydromorphone (Dilaudid) is a metabolite of hydrocodone.
- Given the patient is currently prescribed hydrocodone (Vicodin) there is no clinical intervention needed.

Case 3

- A 36 year-old male patient currently under your care for buprenorphine therapy reports increasing cravings and urges to use. He denies any unauthorized drug use.
- He's currently prescribed Suboxone 8 mg bid and is requesting a dosage increase.
- A UDS is positive for opiates which subsequently shows morphine on GC/MS confirmation.
- The patient adamantly denies drug use.
- What do you do?

Case 3 Discussion

- The presence of morphine in GC/MS confirmation is highly suspicious for heroin use, despite the patient's claim to the contrary.

- Depending on the clinician scenario, it may be prudent to increase buprenorphine dosing to 20 mg daily with close follow-up and frequent drug screens.

Case 4

- A 27 year-old female patient on buprenorphine 8 mg daily and Klonopin 0.5 mg at bedtime has been under your care for 3 months.
- She has been prescribed Klonopin for 10 years and you have agreed to continue this medication under close medical supervision.
- A UDS is positive for benzodiazepines, but you decide to send the sample for GC/MS confirmation which reveals the presence of nor nordiazepam, temazepam, and oxazepam.
- What do you do?

Case 4 Discussion

- Nordiazepam, temazepam, and oxazepam and metabolites of diazepam (Valium).
- Although the patient is prescribed Klonopin and immunoassay was positive for benzodiazepines, the drug test result should be noted as "unexpected."
- The test results should be shared reviewed with the patient.
- Discontinuation of the buprenorphine is not recommended as long as the patient has agreed to participate in dialogue and engage in recommended treatments.

Closing Remarks

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